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CARCINOMA OF THE EYELID*

Analysis of 301 Cases and Review of the Literature

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THE treatment of carcinoma of the eyelid presents many problems not encountered in the treatment of similar lesions elsewhere about the face and other body surfaces. A satisfactory cosmetic result is imperative, and the likelihood of disaster after delayed, inept or unsuccessful treatment is considerable. Several excellent studies have been carried out on this subject, and all workers of considerable experience have reported poor results in patients who have presented themselves with recurrent or persistent disease following previous therapy in other hands. The purpose of this paper is to evaluate the various methods of treatment of primary carcinoma of the eyelid by examination of locally available clinical material and by a review of the experience of others as recorded in the literature.

Carcinoma of the eyelid, like carcinoma of the skin elsewhere, is not a rare disease, occurring more commonly in the male than in the female, and increasing in incidence with age. Different authors have listed chronic irritation, sunlight, chemical irritants, old scars and precursory keratoses as the etiologic factors with about the same conviction as in cancer of the skin on other parts of the body.

The course of the disease is variable. Basal-cell lesions of the eyelid, as in other areas, invade and destroy adjacent tissue by direct extension, but they do not metastasize. Serious sequelae may ensue, however, from their extension from the lid to adjacent structures. Involvement of the bulbar conjunctiva with subsequent destruction of the globe may result, and in cases in which there has been extension into the orbit, incurable involvement of the bony orbit may occur. Lesions about the inner canthus frequently invade the lachrymal duct and may extend directly into the ethmoid sinuses. Hunt[1] states that basal-cell carcinoma of the lid may travel along lymphatics, penetrate the orbital fascia and give rise to orbital extension. Birge[2] found that 25.9 per cent of the basal-cell cases and 6.8 per cent of the mixed group extended into the orbit with ensuing blindness; all the latter group originated at the inner canthus.

Squamous-cell lesions of the eyelid not only spread by direct extension, giving rise to the complication of orbital and sinus invasion, globe destruction and bony involvement characteristic of an untreated basal-cell carcinoma, but also tend to metastasize to the orbit and regional lymph nodes. Birge[2] found that the conjunctiva was involved in 37 per cent of his squamous-cell lesions of the eyelid and that orbital extension almost always accompanied conjunctival and corneal involvement. Hunt[1] reported that 2 of 10 cases metastasized to regional lymph nodes and that the upper and outer lid lesions tended to spread to the preauricular nodes and lesions of the lower lid to the upper cervical nodes. In Martin's[3] experience, the preauricular node is the common site of involvement.

The ultimate course of the disease, like cancer of the skin everywhere, depends in a large part upon its stage of advancement when treatment is undertaken and to a lesser degree upon its location. Small lesions, and others not so small that have not invaded the orbit or sinuses and have not seriously damaged the globe, may be controlled without significant deformity. Uncontrolled lesions may result in the loss of an eye and even in eventual death, owing to local extension or to metastasis in cases of squamous-cell carcinoma. Birge[2] found that the most important factor in prognosis of a basal-cell lesion is its location. In his opinion, cancer of the eyelid is an extremely serious condition because of its ability to blind and kill. He considers the basal-cell lesion a worse "killer" than the squamous-cell lesion, the inner canthus and upper lid to be associated with the greatest mortality, and the

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chance of cure to be negligible if the disease has extended into the orbit. In his series, the mortality from basal-cell lesions was 11 per cent, and that of the entire group of cancer of the eyelid was 12 per cent. His experience with squamous-cell lesions has been wider than that of the other workers cited, and his observations therefore carry weight. In the group of cases with squamous-cell carcinoma of the eyelid the grade of malignancy and the clinical behavior correlated well; the greater the malignancy, the greater the tendency to involvement of lymph node or orbit. Grade IV lesions had the highest death rate, whereas Grade II and III had the highest over-all mortality because of their greater incidence. In Grade I lesions there were no deaths and no loss of the eye. Lesions of the inner canthus proved nearly as dangerous as those of the upper lid.

Martin[3] found a mortality of 6 per cent in his group, the adenoid cystic epithelioma being more malignant than other types as well as being a potentially metastasizing lesion.

Material

The clinical material for this study consists of the hospital records of 301 patients with primary carcinoma of the eye who were seen in the clinics of the Massachusetts General Hospital and of the Collis P. Huntington Memorial Hospital during the twelve-year period from January, 1933, through December, 1944. Only cases in which the carcinoma was primary in the eyelid and in which no previous treatment had been given were included; in all but 1 case the lesions were confined to the eyelid and immediately contiguous structures. Inasmuch as 86 per cent of all recurrences develop within three years of treatment, this particular period was selected so that the minimal follow-up interval would be that in which the recurrence of disease might be expected.

Duration of Disease

The average recognized duration of the disease in the group was three and a half years; the shortest period was one month, and the longest twenty years. This is in fair agreement with the findings of other workers. Birge,[2] in whose series the average duration was over one year, believes that the majority of lesions develop over a long period. Charteris[4] reported a duration of disease from two months to twenty years, and in Hunt's[1] group, 30 per cent of patients had had the disease for over three years.

Age and Sex

Sixty per cent of the lesions occurred in males. The median age of the group was fifty-eight, the youngest being twenty and the oldest eighty-nine. Seventy-five per cent of the group were between fifty and seventy-nine years of age, the peak falling in the sixth decade. If correction is made for normal population decay, however, the incidence is found to increase in a linear fashion after the age of forty.

Incidence of Eyelid Involvement Among All Carcinomas of Skin

During the twelve-year period under consideration, approximately 12,000 cases of cancer of the skin were observed, making the incidence of eyelid involvement 2.5 per cent. Birge[2] reported that cutaneous cancer represented 12 per cent of all epitheliomas, and that 3 to 5 per cent of these were located on the eyelid. The group of 324 carcinomas of the eyelid studied by Driver and Cole[5] constituted 16.8 per cent of 1925 epitheliomas of the skin seen in their clinic.

Table 1. *Topographic Distribution of Lesions.*

Author	Lesions of Lower Eyelid	Lesions of Inner Canthus	Lesions of Upper Eyelid	Lesions of Outer Canthus	Combinations	Others	Totals
Stetson and Schulz	145 (48.2%)	63 (21.0%)	44 (14.6%)	27 (9.0%)	22 (7.2%)	—	301
Martin[3]	80 (54.0%)	41 (28.0%)	19 (13.0%)	7 (5.0%)	—	—	147
Birge[2]	107 (46.5%)	54 (23.4%)	29 (12.6%)	20 (8.7%)	—	20 (8.7%)	230
Lane[6]	149 (46.5%)	90 (18.0%)	52 (10.4%)	32 (6.4%)	89 (18.0%)	88 (17.6%)	500
Hollander and Krugh[7]	47 (37.6%)	52 (41.5%)	17 (13.5%)	9 (7.2%)	—	—	125
Driver and Cole[5]	164 (50.0%)	86 (25.0%)	30 (10.0%)	21 (6.0%)	23 (8.0%)	—	324
Charteris[4]	19 (18.5%)	61 (58.0%)	9 (8.5%)	16 (15.0%)	—	—	105
Hunt[1]	48 (48.0%)	34 (34.0%)	6 (6.0%)	12 (12.0%)	—	—	100
Totals	759 (42.0%)	481 (26.0%)	206 (11.0%)	144 (8.0%)	134 (7.0%)	108 (6.0%)	1,832

Topographic Distribution of Lesions

The lower lid was the most frequent site of involvement (48.2 per cent), and the inner canthus the second most common site (21.0 per cent). The upper lid and outer canthus follow in frequency of occurrence, 14.6 and 9.0 per cent respectively (Table 1). In 22 patients (7.2 per cent), several areas on the lids in the same patient were involved. Six patients exhibited two separate lesions, 3 with bilateral lesions and 3 with the two separate lesions on the same side. In Birge's series, 37 per cent of the squamous-cell cancers arose from the conjunctival surface, including the cornea; primary corneal squamous-cell neoplasm was rare.

Histology of Lesions

The diagnosis in 162 cases (54 per cent of the entire group) was confirmed by biopsy; in the remaining 139 cases the diagnosis was clinical only, the lesions bearing the expected characteristics of basal and squamous-cell carcinoma. Of the 162 histologically proved cancers (Table 2 and 3), 82 per cent were basal-cell (4 of the hair-matrix type), 14.5 per cent squamous-cell, and 2.4 per cent basal-cell and squamous-cell lesions, and 1.2 per cent adenoid cystic epitheliomas. Rare carcinomas arising in meibomian glands have been reported by Hagedoorn[8] and Lebensohn[9]; none were observed in this series. Neither in the present group nor in the cases reported by Birge[2] or Hunt[1] did there seem to be any predilection of site for any particular type of tumor.

TABLE 2. *Histopathological Classification of Lesions.*

Author	Total No. of Cases	Lesions Biopsied	Basal-Cell Lesions	Mixed Lesions	Squamous-Cell Lesions						Adenoid Cystic Lesions	Others
					Totals	Grade I	Grade II	Grade III	Grade IV	Ungraded		
Stetson and Schulz	301	162 (54.0%)	133 (82.0%)	4 (2.4%)	23 (14.5%)	18	2	3	—	—	2 (1.2%)	—
Birge[2]	464	230 (49.5%)	139 (60.0%)	32 (14.0%)	59 (25.0%)	8	21	18	6	6	—	—
Martin[3]	147	—	125 (85.0%)	—	15 (10.0%)	—	—	—	—	—	7 (5.0%)	—
Hollander and Krugh[7]	125	60 (48.0%)	45 (75.0%)	1 (1.6%)	13 (21.6%)	—	—	—	—	—	—	1 (1.6%)
Driver and Cole[5]	324	109 (33.6%)	73 (66.0%)	9 (8.2%)	20 (18.2%)	—	—	—	—	—	7 (6.4%)	—
Hunt[1]	100	61 (61.0%)	48 (78.7%)	3 (4.9%)	10 (16.4%)	—	—	—	—	—	—	—

Treatment and Results

In 76 per cent of the entire group, irradiation treatment was used. The majority of 23 patients treated with 100 kv. r received a single large dose. Of the 111 treated with 200 kv., 75 per cent were given a single large dose, and 25 per cent fractionated doses. The effective tumor dose was about 3000 r. When radon was applied topically, the average skin dose was 3275 gamma r. Seventy-one patients were treated surgically (electrosurgery or surgical excision).

Table 4 records the methods and results of treatment. The results are based on patients of the entire group who had been followed three years or longer, since it was found that in 86 per cent a recurrence, if there were one, developed within three years. Figure 1 and 2 demonstrate the results in 2 cases eight and twelve years, respectively, after treatment. Of the 21 cases in which there was a recurrence of disease, it appeared within a year in 38 per cent, between one and two years in 24 per cent, and between two and three years in 24 per cent. In 2 cases the disease recurred in the fourth year, and in only 1 was the recurrence as long as the fifth year after treatment. The average follow-up period was six and three-tenths years.

The results of treatment were classified as follows: "cure" from primary treatment; "cure" after subsequent treatment; and failure (from recurrent disease, from persistent disease and from metastasis). The term "cure" is applied to cases in which there was no apparent disease during the follow-up period. "Recurrent disease" indicates recurrence in a previously treated area after an interval of at least three months following therapy during which no disease had been evident. "Persistent disease" denotes that the disease at no time appeared to be completely eradicated.

From a percentage standpoint, no significant difference was noted in the number of failures of the various treatments employed. In an attempt to determine the causes of the unsatisfactory results of the primary treatment, it was found that inadequate radiation, or inadequate excision in patients treated surgically, headed the list. In 5

TABLE 3. *Histopathological Distribution of Lesions.*

Site of Tumor	Total No. of Cases	Basal-Cell Carcinomas			Mixed Carcinomas			Squamous-Cell Carcinomas			Adenoid Cystic Carcinomas		
		Stetson and Schulz	Birge[2]	Hunt[1]	Stetson and Schulz	Birge[2]	Hunt[1]	Stetson and Schulz	Birge[2]	Hunt[1]	Stetson and Schulz	Birge[2]	Hunt[1]
Total cases of all types	453	162	230	61									
Lower eyelid	213	65	76	20	1	14	2	10	17	6	2	—	—
Inner canthus	108	25	37	20	2	9	1	4	8	2	—	—	—
Upper eyelid	60	24	14	—	1	5	—	6	10	—	—	—	—
Outer canthus	38	7	12	8	—	4	—	1	4	2	—	—	—
Combinations	14	12	—	—	—	—	—	2	—	—	—	—	—
Others	20	—	—	—	—	—	—	—	20	—	—	—	—
Totals	453	133 (82%)	139 (61%)	48 (79%)	4 (2%)	32 (13%)	3 (5%)	23 (15%)	59 (26%)	10 (16%)	2 (1%)	—	—

cases failure was due in part to error in x-ray technic (the size of the field was inadequate to cover the lesion). In 6 of the surgically treated cases, inadequate excision was demonstrated by recurrence of the disease in the suture line. The tumor proved radioresistant in 11 cases, — for example, a superficial lesion 0.5 cm. in diameter did not respond to a single dose of 3000 r (air). In one case the appearance of metastases accounted for failure; another failure was due to the fact that at the time the patient was first seen the disease had extended into the bony orbit.

From the standpoint of topographic distribution, there was nothing to indicate that the position of the lesion had any bearing on an unsatisfactory result, provided the disease had not already become uncontrollable because of extension to lymph nodes, the orbit or the sinuses. The histologic characteristics of the tumor, however, appeared to be of significance. Failure of the primary treatment was twice as frequent in squamous-cell lesions as in basal-cell lesions. The 5 cases that were ultimate failures are briefly reported as follows:

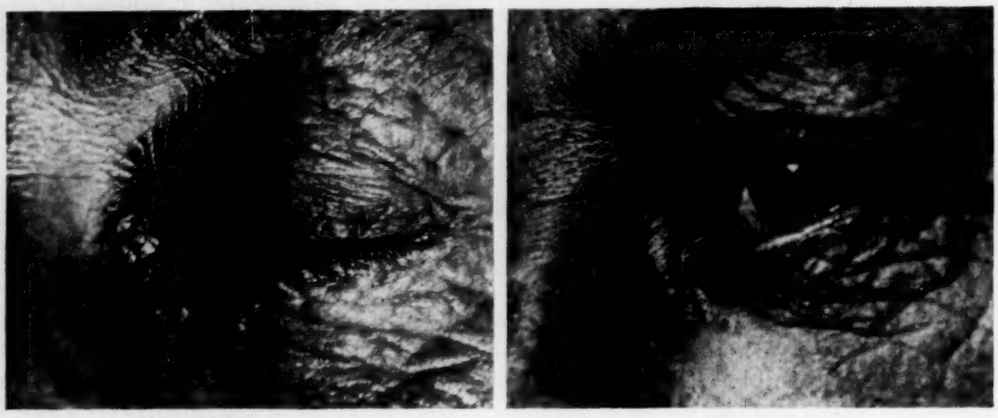
CASE 1. An uncontrolled recurrence in a 79-year-old m resulted from inadequate excision of an 0.5 cm. basal-cel lesion of the upper eyelid. The recurrent growth, which de veloped 5 months after excision, was re-excised and showed a mixed squamous-cell and basal-cell tumor. The disease then extended into the orbit and was treated with 200 kv x-ray. This was classed as a surgical failure. (The patient died 3 years after the first excision from rupture of multiple hemangiomas of the gastrointestinal tract.)

TABLE 4. *Methods of Treatment and Comparative Results in 219 Cases Followed.*

TREATMENT	TOTAL NO. TREATED	CURES*			FAILURES			
		BY PRIMARY TREATMENT	AFTER SECONDARY TREATMENT	TOTALS	TOTAL NO.	RECURRENT DISEASE	PERSISTENT DISEASE	METASTATIC DISEASE
Radon	25	22	3	25 (100%)	0	0	0	0
Radium	3	2	1	3 (100%)	0	0	0	0
X-ray (100 Kv.)	23	20	3	23 (100%)	0	0	0	0
X-ray (200 Kv.)	111	96	11	107 (97%)	4 (3.0%)	0	3	1
Surgery	57	50	6	56 (99%)	1 (1.0%)	1	0	0
Totals	219	190	24	214 (97.5%)	5 (2.5%)	1	3	1

*No evidence of disease after treatment for the period of follow-up study.

CASE 2. A 69-year-old man presented total involvement of all lids, globe and orbit at the time of his initial visit. Biopsy revealed a squamous-cell cancer, Grade III. He received fractionated daily 200 kv. x-ray therapy, to a field 10 by 10 cm., a total dose of 3000 r measured in air being given. He refused further treatment. He was known to be living five years after treatment and was assumed to have residual disease. In all probability the disease was incurable at the time he was first seen, but adequate palliation was obtained.



A B

FIGURE 1. *Photographs of Patient J. J. (U-328878), with a Basal-Cell Carcinoma about the Inner Canthus Involving the Punctum, Who Was Treated with 500 r per Day for 3500 r with 200-kv., 0.25-mm. Copper Filter at a Skin-Target Distance of 20 cm.*

A *shows the lesion before treatment, and* B *three years after treatment. The patient was well and free of disease eight years after treatment, with only slight tearing as an undesirable complication.*

CASE 3. A 54-year-old man had persistent uncontrolled disease from an 0.5-cm. basal-cell carcinoma at the inner canthus. He refused to accept more than a single treatment, and was given 3500 r (air), 200 kv. x-rays with 0.25-mm. Cu and 1-mm. Al filters being used. Nine months later, when he was persuaded to return to the clinic, there was clinical evidence of residual disease. The final outcome is unknown since the patient refused both further treatment and further follow-up study.

CASE 4. An 84-year-old, extremely feeble woman had a squamous-cell carcinoma, Grade III, involving the entire

lower lid. She refused hospitalization, and was treated with x-rays generated at 200 kv., filtered with 0.25 mm. Cu and 1 mm. Al. At weekly intervals 400 r, measured in air, was given to a total dose of 1200 r (air). The patient was unable to return for further treatment because of increasing feebleness and died from bronchopneumonia 5 months from the date of her initial visit. She might have been cured.

CASE 5. A 57-year-old man died from metastatic disease from a Grade I squamous-cell lesion on the outer aspect of the upper lid. The primary cancer was destroyed by daily treatments of 600 r (air) to a total dose of 4200 r (air), 200 kv. x-ray therapy with 0.25-mm. Cu, 1-mm. Al filters at skin-target distance of 50 cm. being used. Eight months later, adenopathy of the upper cervical lymph nodes on the side of the original lesion developed; biopsy showed metastatic squamous-cell carcinoma. The metastases were considered to be too extensive for a radical neck dissection, particularly as the patient was a poor surgical risk. The nodes were irradiated with 200 kv., but the patient went downhill rapidly and died 18 months after the initial treatment to the eyelid. This case might have been salvaged had the cervical involvement been noted at an earlier date.

A B

FIGURE 2. *Photographs of Patient A. S. (U-346117), with a Squamous-Cell Carcinoma Involving the Inner Canthus and Punctum, who was Given a Single Treatment of 2000 r with 200-kv., 0.25-mm. Copper Filter at a Skin-Target Distanco of 20 cm.*

A *shows the appearance before treatment, and* B *three years after treatment. The patient was well twelve years after treatment, with only slight telangiectatic formation at the lid margin.*

The results of treatment in this study are not comparable to those of other workers, since only patients who received their primary treatment in this clinic were included. It is interesting to note, however, that good results in the treatment of this disease have been reported by most of the clinics whose work has been published. Hollander and Krugh[7] had good results in 97 of 125 cases and unsatisfactory results in 28; they concluded that no method of treatment is superior to any other.

Driver and Cole,[5] in a follow-up study of 291 patients for one month or over, found 19 (6.5 per cent) recurrences and 272 (93.5 per cent) possible cures. There were 6 deaths from the disease. Among 193 cases followed for six months to ten years there were 12 relapses. Relapses after five years were rare; 181 cases, or 93.8 per cent, were possible permanent cures.

In 76 cases treated with radium, Charteris[4] reported 2 failures, 6 patients requiring secondary treatment and 68 or 89.4 per cent with good results from the primary treatment.

Richards[10] had 3 failures out of 102 cases treated; in 2 of the failures previous treatment had been given. Martin[3] did not find five-year results revealing; he believed that the end-results must be evaluated on the basis of function and appearance. In 85 per cent of his patients the first treatment was successful; 7 per cent required more than one treatment, and 6 per cent died of their disease.

Birge[2] followed 127 of 139 basal-cell carcinomas of the eyelid and found an 11 per cent mortality. In the basal-cell group, 46.1 per cent of patients lived fifteen years or more; 75 per cent with the mixed type of carcinoma lived fifteen years or longer. Of the squamous-cell cancers, 50 per cent recurred, Grade III showing the greatest tendency to recurrence. There were no deaths in the Grade I (squamous-cell) group; 15 per cent of patients with Grade II lesions died, and among those with Grade III tumors there was a 46 per cent death rate. The orbit was involved in 30 per cent of the Grade II squamous-cell group and in 53 per cent of Grade III; in Grade IV, the orbit was invaded in every case, and no patient survived five years.

COMPLICATIONS OF TREATMENT

Complications of treatment of carcinoma of the eyelid — that is, undesirable by-effects incident to treatment that would otherwise have been considered satisfactory — are not numerous. Complications that follow surgical treatment are primarily unsightly scars or defects requiring plastic revision and lid-drop due to interference with the innervation or attachment of the elevator of the lid. Among 71 patients treated by means of surgical operation, 1 case of each of these complications occurred.

Undesirable side effects are more common after irradiation. The most frequent of these is stenosis of the tear duct when lesions involving the inner canthus and medial portions of the lids are treated. Out of 31 cases in which the inner canthus was irradiated, stenosis of the tear duct developed in 8, or 26 per cent. This complication is at times unavoidable, especially when the neoplasm has already invaded and destroyed the duct. Since lesions in this location do not lend themselves to surgical intervention, a certain number of stenosed ducts must be expected and accepted as the legitimate price paid for control of the disease.

It is the opinion of some investigators that attempts should be made to dilate and keep open the stenosed and destroyed duct. This procedure, however, is of benefit only in cases in which the stenosis is not complete and in which the duct has not been entirely destroyed by tumor.

The formation of cataract is a serious post-radiation complication and has often been reported. It should never occur, however, when the lesion is treated with x-rays and the globe has been properly protected with a lead shield. Protection of the lens when radium is used is difficult. In our series no case of radiation cataract has been observed. This is accounted for in part by the fact that the eye has always been carefully shielded during x-ray therapy. Radium and radon have been employed only in a limited and selected group of patients. A radium plaque was used once, interstitial radium needles three times, and interstitial radon seeds on two occasions, and in 35 other cases surface application of radon was utilized for superficial lesions, the average skin dose not exceeding 3300 r.

Several interesting observations have recently been reported concerning the time factor in the development of radiation cataract and the amount of radiation necessary to produce it. Hunt[1] found the average latent period to be twelve years, although the complication might develop in three months. He reported 5 cases in which lens opacities developed, 2 from radium and 3 from unshielded x-ray therapy (there were none in the shielded cases). He calculated the dose received by the lens in the 3 cases treated by radium to be 2400, 1500 and 1350 r, the opacities developing after six months, eight years and five years respectively. Of the 2 opacities that followed x-ray therapy, the dose in 1 was 875 r (air), 130-Kv x-ray, 1-mm. Al filter, and in the other 4800 r in 6 treatments from 130-kv. x-ray, 1-mm. Al filter; both were unshielded.

Martin[3] states that cataracts may develop in twelve to thirty-six months after radiation. In Smithers's[11] experience, a five-year latent period is not uncommon. Charteris[4] believes that eye damage is unlikely if the dose is below 2800 r although it may follow 1500 r. He found the implantation of radium to be most dangerous when applied to an upper-lid lesion. Of his 76 patients treated by radium, 11 showed late ocular changes, 7 of which he attributed to radiation (4 lost their vision). Richards[10] believes that cataract develops only as a result of long-continued use of hard rays.

In our opinion proper care and meticulous attention to details of technic when carcinoma of the eyelid is treated by x-rays should eliminate this hazard completely, except in cases in which extensive tumor involvement of the orbit and globe makes it impossible to protect the eye itself. In the 2 patients in the present series in whom destruction of the globe, subsequently necessitating enucleation, occurred there was extensive involvement of the bulbar conjunctiva at the time the patient was first seen, making protection of the eye impossible.

Persistent chronic, painful conjunctivitis following x-ray treatment has been observed only once in this group. Corneal ulcer, a theoretical complication of radiation, has never been seen. Proper protection of the globe and careful shielding of the adjacent normal tissues with lead should allow irradiation without damage to bulbar conjunctiva or cornea.

Severe deformity of the lids requiring plastic repair, observed in only 3 of the cases treated by radiation, occurs only when the disease is advanced and there is already destruction of tissue by tumor.

Discussion

Good results in the treatment of carcinoma of the eyelid can be obtained by any of the available methods in skilled hands. Prior to any form of treatment, after the diagnosis has been established, the patient should have a thorough examination by a competent ophthalmologist. It is important to have a record of these findings in the event of subsequent ocular complications. In all fixed lesions about the lid, adequate x-ray studies of the sinuses and orbit, to rule out possible bony involvement, should be made. This is particularly necessary in infiltrating and fixed lesions about the inner canthus, which are prone to extend into the ethmoid sinuses; it is mandatory in cases in which the globe or orbital tissues are invaded by disease.

A capable plastic surgeon may obtain good results by the excision of small lesions. Against this choice of treatment stands the fact that there is often considerable nonvisible tumor infiltration, which results in recurrence of tumor in the suture line. Surgery plays an important role in a selected number of patients who have extensive involvement of the globe or orbit. Radical exenteration of the orbit may be required; the globe as well as other orbital tissues must be removed in case of involvement. When residual disease is suspected, radiation to the orbit should follow surgical operation.

Prior to the acquisition of suitable low-voltage therapy, most of the superficial lesions of the eyelid were treated by surface application of radon. Only limited use has been made of surface and interstitial

therapy with radium element. At the present time the routine use of radium with its possible sequelae does not seem justified when equally good results can be obtained with roentgen-ray therapy without the danger of damage to the eye.

If x-radiation is to be employed, the first consideration is protection of the eye. For low-voltage x-ray treatment Hunt[1] used a 1.2-mm. lead shield coated with nickel. He found that a 1-mm. lead shield removed 97 per cent of the radiation from 140-kv. x-rays, filtered with 0.25-mm. Cu and 1-mm. Al. Smithers[11] points out that complete protection is impossible when the tumor has invaded the eyeball or orbit and states that the risk of damage to the eye from treatment must be considered as of secondary importance. When the tumor is limited to the lid, he uses for low-voltage therapy an accurately ground contact glass lens covered by 1 mm. of lead. He states that less than half of 1 per cent of low-voltage radiation will penetrate this shield. He also describes a very practical type of plastic Perspex eyeshield covered by 1 mm. of lead; this is available in multiple sizes and contours. Driver and Cole[5] prefer lead shields coated by paraffin.

For the treatment of most primary carcinomas of the eyelid x-ray therapy seems to be the method of choice. The occurrence of failures or other undesirable results is no greater than with other forms of therapy; the discomfort to the patient is not great, and the cosmetic and functional results are equal to or better than those obtained by other means. An accepted technic of procedure, found to be satisfactory, is described below.

Technic of Irradiation of Eyelid

The eyeball is anesthetized, and a 2-mm. lead shield coated with paraffin is inserted. The size of the shield is adequate to include a margin of normal surrounding tissue. An excellent protective device for lesions of the inner canthus is a lead nipple shield (Fig. 3C). These nipple shields are no longer available commercially, but they can be easily made.

For small lesions, x-rays at 100 kv., unfiltered, with a skin-target distance of 20 cm. are used. A single treatment of 2700 to 3000 r (air) may be delivered, or the fractionated technic may be employed. It is thought that the latter gives better cosmetic results. For the treatment of a small lesion with the fractionated method, daily doses of 1200 to 1500 r (air) are given to a total of 3600 to 4500 r (air). When the lesion is more extensive the daily dose may be reduced to 500 r (air) and carried to a total dose of 5000 to 6000 r (air).

For treatment of an infiltrating and fixed lesion, particularly one in the region of the inner canthus, 140-kv. to 200-kv. x-rays filtered by 0.25-mm. Cu and 1-mm. Al are used. The treatment is fractionated.

For a lesion that has involved the bony orbit or ethmoid sinus by extension, 200-kv. x-rays with 0.5-mm. Cu and 1-mm. Al filters are employed.

Experience with Phillips contact therapy has not been of sufficient duration to evaluate results. It appears to have a definite place in the therapeutic armamentarium available for the treatment of carcinoma of the eyelid, although its use should probably be reserved for superficial lesions.

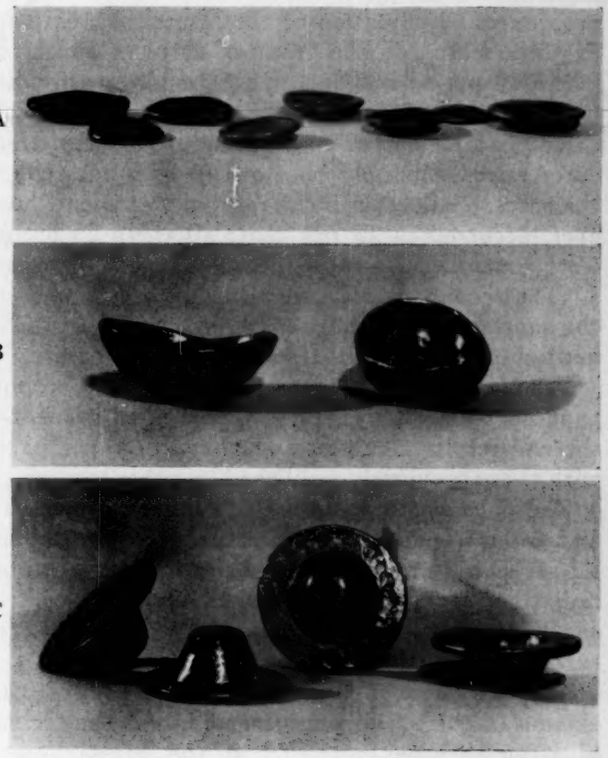


FIGURE 3. *Protective Shields for Lesions of the Inner Canthus. A shows various sizes and shapes of paraffin-covered lead shields, designed to fit beneath the lid and over the globe. These are made by hammering of pieces of lead, 2 mm. thick, between the ball and peen of a mechanic's hammer. B illustrates larger lead shields, designed to fit over the lid and globe of the eye and made in essentially the same manner. C shows old-fashioned lead nipple shields, with holes of various sizes bored in their tips, used in the treatment of lesions about the inner canthus.*

SUMMARY AND CONCLUSIONS

The experience with treatment of carcinoma of the eyelid at the Massachusetts General Hospital and at the Collis P. Huntington Memorial Hospital during the twelve-year period from 1933 through 1944 is summarized, and the pertinent literature is reviewed.

The study was based on 301 cases of primary carcinoma of the eyelid having an average duration of three and a half years. Sixty per cent of the lesions occurred in males; the median age of the patients was fifty-eight years. Carcinoma of the eyelid

represented an incidence of 2.5 per cent of all skin cancers observed during the same period.

The lower lid was the most frequent site of involvement; the inner canthus was the second most common. Histologic examination showed that 82 per cent of the biopsied lesions were basal-cell carcinomas; 14.5 per cent were squamous-cell tumors.

The methods and the results of treatment are analyzed; 76 per cent of patients received irradiation, and 24 per cent were treated by surgical procedures. Evaluation of the results of treatment has been based on the group of cases in which the follow-up period was three years or longer; primary failure to control the disease was manifest within three years in 86 per cent of the group. Apparent cures were ultimately obtained in 97.5 per cent of the cases. Failures from the initial treatment, however, occurred in 13 per cent; all these 29 lesions were controlled by subsequent management except 5. The secondary treatment in most cases was not the same as the primary treatment had been. The net failures comprised 2.5 per cent of the cases.

From a percentage standpoint there was nothing to indicate that the method of treatment influenced the end-results. These results have been compared with those previously published by other workers.

The chief complications of treatment were scars and defects from surgical operation requiring plastic revision and stenosis of the tear duct following radiation therapy of lesions involving the inner canthus. No cases of radiation cataract have been encountered in this clinic.

The available methods of treatment of carcinoma of the eyelid are discussed, and the technic of x-ray therapy employed at the Massachusetts General Hospital outlined.

Primary carcinoma of the eyelid when limited to the lid has an excellent prognosis if the treatment is adequate. Even in the event of initial failure to control the disease, subsequent treatment is usually successful.

Squamous-cell carcinoma of the eyelid is more refractory to treatment and results in more complications than basal-cell carcinoma, and therefore has a poorer prognosis.

In the treatment of primary carcinoma of the eyelid, good results can be obtained by any of the available methods of treatment judiciously applied. The facility of treatment by x-radiation and the excellent cosmetic and functional results that usually follow make it, as a rule, the treatment of choice.

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CHLOROMYCETIN IN THE TREATMENT OF PNEUMONIA IN INFANTS AND CHILDREN*

A Preliminary Report on Thirty-Three Cases

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CHLOROMYCETIN is an antibiotic derived from a strain of *Streptomyces venezuelae*. Its antimicrobial spectrum is broad and embraces the following organisms: rickettsia, certain viruses of the psittacosis group, gram-positive cocci (including the pneumococcus, streptococcus and staphylococcus) and certain gram-negative organisms including *Eberthella typhosa*, shigella and several of the coliform group.[1] The drug is well tolerated orally, and few toxic reactions have followed its use in therapeutic doses. Chloromycetin is readily absorbed after oral administration, and blood levels of 10 to 40 mg. per 100 cc. are readily obtained when 50 to 100 mg. per kilogram of body weight are administered daily to children in a four-hour to six-hour divided-dosage schedule.[2] The drug is also absorbed moderately well after rectal administration, the level, to a first approximation, representing 20 to 50 per cent of the absorption obtained after oral administration.[2] In view of the insolubility of chloromycetin in water or saline solution, parenteral administration of the drug is not feasible.

The sensitivities to chloromycetin of the pneumococcus, streptococcus, staphylococcus and *Haemophilus influenzae* have been found in vitro to range between 0.5 to 5 microgm. per cubic centimeter — concentrations that are readily exceeded with therapeutic doses of the drug orally. Since these organisms constitute the most common etiologic agents of bacterial pneumonia in infants and children a clinical trial of the drug in the disease appeared to be indicated. Thus, during the winter of 1948–1949, a special pneumonia ward was set up at the Children's Hospital, Washington, D. C., to study the efficacy of chloromycetin (as well as aureomycin) in the treatment of pneumonia. During a four-month period, 39 patients were treated with aureomycin,[3] and 33 with chloromycetin. The present report deals with the results obtained in the latter group.

*From the Research Foundation, Children's Hospital.

This study was supported by a grant to the Children's Hospital from the Antibiotic Study Section of the Division of Research Grants and Fellowships, The National Institutes of Health, United States Public Health Service, and was conducted under the auspices of the Antibiotic Committee of Children's Hospital consisting of Drs. E. Clarence Rice, Frederic G. Burke and John A. Washington.

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METHOD OF STUDY

A uniform diagnostic workup was employed in each suspected case of pneumonia. This consisted of an x-ray examination of the chest, complete blood count, nasopharyngeal and blood cultures and agglutinins for streptococcus MG and cold hemagglutinins. After this initial study, repeat chest films, blood counts and nasopharyngeal cultures were taken every two or three days during the course of therapy, and the serologic studies were performed at intervals of seven to fourteen days. Strict clinical and laboratory criteria were employed before a case was included in this study, and any patient who presented equivocal findings on admission was summarily excluded from this series.

Thirty-three patients fulfilling the established diagnostic requirements of pneumonia were treated with chloromycetin. The ages of these children ranged from four months to twelve years. Of these, 3 patients were less than six months, and 6 ranged from six to twelve months, 8 from one to two years, 5 from two to six years, and 11 from six to twelve years of age.

The 33 cases in this series, all of which were considered to be bacterial pneumonias, were classified as follows: pneumococcal 18; streptococcal, 1; staphylococcal, 1; and unclassified, 13. A pneumococcus was the sole or predominating organism on the nasopharyngeal cultures of the first group, a finding that was considered strong evidence that this organism represented the pathogen in the lower respiratory tract. Beta-hemolytic streptococci in large numbers were cultured from the nasopharynx of 1 patient, and *Staphylococcus aureus* was isolated from the throat and empyema fluid of another. Nasopharyngeal cultures in the other 13 cases of pneumonia yielded *Staph. aureus*, *Staph. albus*, *Streptococcus viridans*, *Neisseria catarrhalis* and *H. influenzae*, and the cases were therefore placed in the unclassified group. This is predicated on the fact that, with the exception of the pneumococcus, the isolation of an organism from the nasopharynx is not necessarily presumptive evidence that it represents the pathogen in the lower respiratory tract.[4] It is possible that in several of the unclassified group, the organism isolated on nasopharyngeal culture was indeed the cause of the pneumonia, particularly in the 4 cases in which

H. influenzae was the predominant organism. However, definite proof was lacking, and thus the unclassified group constitutes a singularly large percentage of the total number of cases. In spite of the inability to indict a specific organism as the causative agent, the clinical manifestations together with the roentgenologic findings and leukocytosis were all compatible with a diagnosis of bacterial pneumonia in this unclassified group.

Twenty of the 33 patients were considered to be markedly ill at the time of admission, and 8 of these required oxygen. Eleven of the remaining 13 were regarded as moderately ill, and the other 2 cases were classified as mild. The temperature at the time of initiation of chloromycetin therapy ranged from 101 to 106°F. In 27 of the 33 cases, it was above 103°F. In 16 patients (48 per cent) the white-cell count at the time of hospitalization was above 20,000, and in 15 cases it ranged from 10,000 to 20,000. Two other patients showed white-cell counts below 10,000. In each patient in this series there was demonstrable x-ray evidence of pneumonia.

Dosage of Chloromycetin

Chloromycetin* was administered orally in a dosage ranging from 50 to 220 mg. per kilogram of body weight per twenty-four hours, or an average of 112 mg. per kilogram per day. The dosage interval was usually every three hours, an occasional patient receiving the drug every four hours. The duration of therapy ranged from two to six days, with an average of four and eight-tenths days per patient. The total dose of chloromycetin ranged from 3.4 to 11.3 gm., with an average of 5.9 gm. per patient.

Table 1. *Results in 33 Cases of Bacterial Pneumonia Treated with Chloromycetin.*

Type of Pneumonia	Good Results	Fair Results	No Effect
	no. of cases	no. of cases	no. of cases
Pneumococcal	13	5	—
Streptococcal	1	—	—
Staphylococcal	—	—	1
Unclassified	11	2	—
Totals	25	7	1

With reference to the administration of chloromycetin orally, only in the older age group was it possible to administer an intact capsule. In infants and younger children, it was necessary to empty the contents of the capsule and, in view of the extreme bitterness of the drug, to administer it in different vehicles. These included syrup of Santa Yerba, chocolate milk, chocolate syrup, cherry syrup, applesauce and lemon juice. Our experience in this regard indicated that mixing the drug with syrup of Santa Yerba and following it with chocolate milk was perhaps the best method of administration in small children.

*Supplied by Parke-Davis Company, Detroit, Michigan, through the courtesy of Dr. E. A. Sharp.

Results

The therapeutic effect of chloromycetin on the 33 patients with bacterial pneumonia was favorable. The over-all results (based principally on the rapidity of return to normal of clinical, roentgenologic and laboratory findings) were considered good in 25 cases, fair in 7 and poor in only 1 (Table 1). In 1 case a relapse occurred a week after the drug had been discontinued, and the patient was retreated with chloromycetin. An uneventful recovery ensued. One patient who had a staphylococcal pneumonia with an associated empyema showed no improvement with chloromycetin after forty-eight hours. Penicillin and aureomycin were then substituted, but the patient failed to improve until surgical drainage was performed.

In 20 of the 33 patients the temperature returned to normal within eighteen hours of the initiation of chloromycetin therapy (Fig. 1). In 7 other patients defervescence was observed eighteen to thirty-six hours after treatment had been started. In 5 of the 6 remaining cases, the temperature was normal after thirty-six to seventy-two hours. Thus, in 32 of the 33 cases, the temperature was normal within three days of the initiation of therapy. Concomitantly, there was striking clinical improvement characterized by prompt relief of the prostration, dyspnea and cough.

The rapidity of clearing of the nasopharyngeal pathogens following initiation of chloromycetin was observed by the performance of serial nasopharyngeal cultures on each patient. The first culture was obtained at the time of admission, and two to four subsequent cultures were obtained at two-day intervals. In 9 of the 18 cases of pneumococcal pneumonia, the organism was not demonstrable after the second day of therapy. In 2 other patients, the organisms had disappeared by the fourth day. In the remaining 7, pneumococci (usually in reduced number) were still demonstrable on nasopharyngeal culture after the fourth day. Of the 4 cases in which *H. influenzae* was the predominant organism on the initial culture, 3 were negative for this organism two days after chloromycetin therapy had been started. In the case in which a hemolytic streptococcus was the sole organism isolated from the nasopharynx prior to treatment, the organism disappeared two days after therapy had been begun.

An analysis of the drop in white-cell counts revealed that in 21 of the 33 patients the count had returned to normal by the third day after the initiation of chloromycetin therapy. Of ancillary interest was the observation that in several cases

the white-cell count dropped below 4000 three to five days after therapy had been started. However, the leukopenia was not progressive and was not associated with any granulocytopenia. In no case was it necessary to discontinue the drug because of the leukopenia. There was no concomitant reduction in red-cell or platelet count.

Serial chest x-ray films showed appreciable resolution of the inflammatory process four to seven days after chloromycetin had been started in 24 out of the 33 patients.

Data on the therapy and results in 18 cases of pneumonia are presented in Table 2. The following cases serve to illustrate the response to chloromycetin.

T. E., an 11-month-old Negro boy, was admitted to the hospital with a 2-day history of fever, progressive cough and rhinorrhea.

Physical examination revealed an acutely ill and dyspneic infant with a temperature of 104°F. by rectum. Fine crackling rales were heard in the right axilla and over the right lower portion of the chest posteriorly. The remainder of the examination was essentially negative.

The white-cell count on admission was 15,400, with 73 per cent neutrophils. Beta-hemolytic streptococci were cultured from the nasopharynx. A blood culture was sterile. Cold hemagglutinins and streptococcus MG titers were negative. X-ray study of the chest disclosed a disseminated area of infiltration in the right-lung field.

Chloromycetin therapy was instituted on admission in a dose of 250 mg. initially followed by 125 mg. every 3 hours. The infant improved rapidly and in 12 hours was afebrile and considerably improved clinically. The white-cell count dropped very quickly; on the 2nd day it was 6000, with 40 per cent neutrophils, and on the 5th day it was 3700 with 22 per cent neutrophils. Nasopharyngeal cultures on the 3rd and 6th days yielded no pathogens. Repeat chest x-ray examination on the 5th day revealed no appreciable resolution. Chloromycetin was discontinued after 4½ days, and the patient was discharged on the 7th hospital day after an uneventful recovery. Figure 2 shows the course in the hospital.

He was examined in the follow-up clinic 2 weeks after leaving the hospital and found to be in good condition. Repeat cold hemagglutinins and streptococcus MG titers at this time were negative.

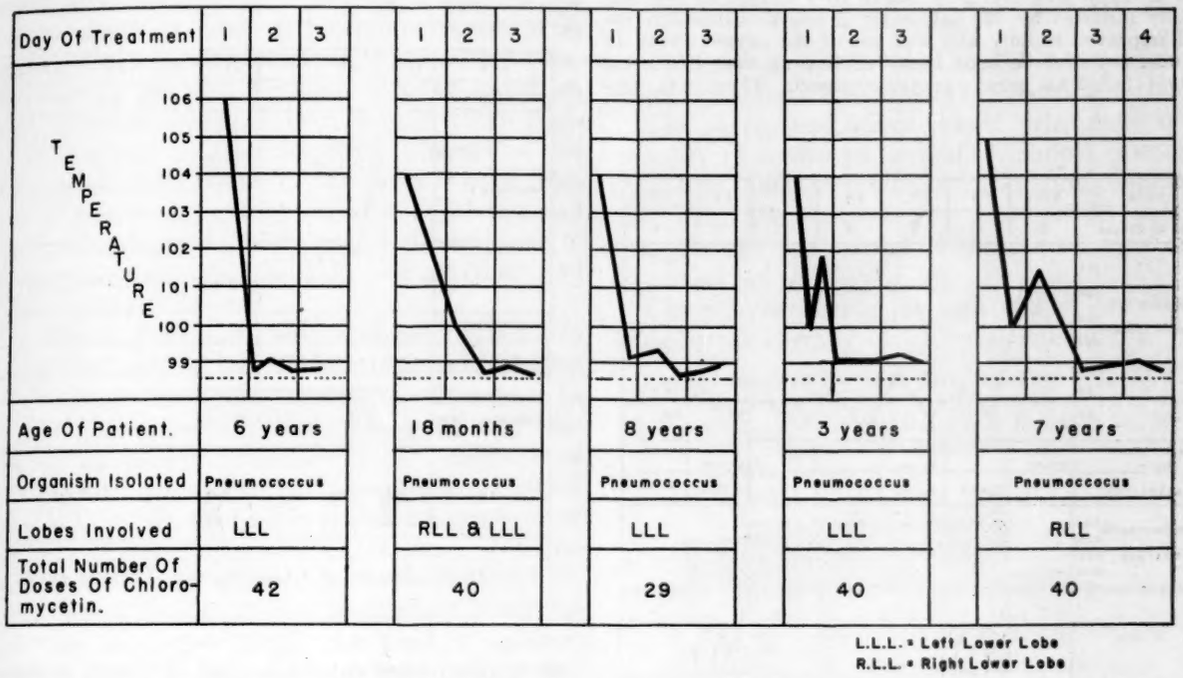

FIGURE 1. *Representative Cases of Pneumococcal Pneumonia Treated with Chloromycetin.*

R. J., a 2-year-old Negro boy, had had a high fever, cough and anorexia 2 days before entry. These symptoms progressed during the next 48 hours, at which time hospitalization was advised.

Physical examination revealed an acutely ill child with a temperature of 104.6°F. by rectum, a pulse of 136 and respirations of 72 per minute. The pharynx and the right eardrum were injected. Over the left posterior portion of the chest there were dullness to percussion, increased breath sounds and fine crepitant rales on auscultation.

TABLE 2. *Data in 18 Cases of Pneumococcal Pneumonia Treated with Chloromycetin.*

CASE NO.	AGE	CHLOROMYCETIN THERAPY			RESULT
		DAY INITIATED	DOSE	TOTAL DAYS	
	yr.		mg./kg./24 hr.		
1	2 2/12	4	83	3	Good
2	1 2/12	3	83	4	Fair
3	5/12	4	168	6	Fair
4	7/12	4	212	5	Good
5	7	2	84	5	Good
6	1 7/12	3	106	5	Good
7	1 6/12	4	88	5	Good
8	12	6	50	5	Good
9	8	4	55	6	Good
10	8/12	3	125	5	Good
11	6	3	115	6	Good
12	3	2	107	5	Good
13	5/12	2	220	5	Fair
14	7/12	3	105	6	Fair
15	1 11/12	3	100	5	Good
16	6	6	210	4	Good
17	3	5	132	5	Good
18	4/12	4	200	6	Fair

X-ray study of the chest disclosed a diffuse inflammatory process throughout most of the left lung indicative of bronchopneumonia.

Pneumococci were isolated from the nasopharynx, and a blood culture was sterile. The white-cell count on admission was 24,400, with 90 per cent neutrophils. Cold hemagglutinins were present in a dilution of 1:128, and streptococcus MG agglutinins in a dilution of 1:10.

The patient was placed in an oxygen tent, and chloromycetin therapy was promptly begun in a dosage of 250 mg. initially followed by 125 mg. every 3 hours. Clinically, the child improved rapidly and was out of the oxygen tent in 24 hours and afebrile in 36 hours. Follow-up nasopharyngeal cultures failed to grow out pneumococci. There was considerable clearing of the area of infiltration on x-ray examination within 3 days and complete resolution in 6 days. The white-cell count returned to normal in 3 days.

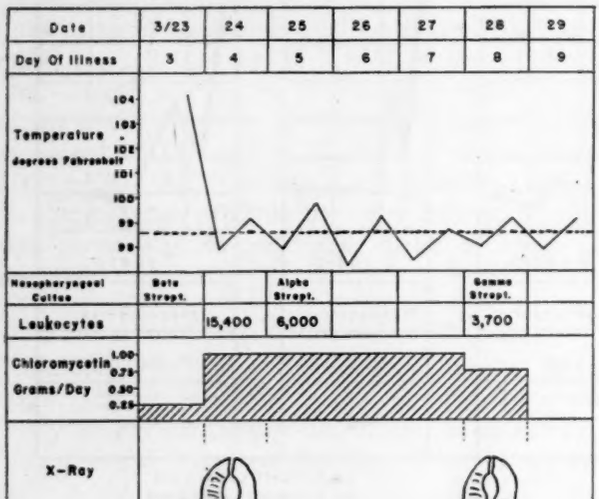

FIGURE 2. *Results of Chloromycetin Therapy in T. E.*

Chloromycetin was discontinued after 4 days, and the patient was discharged in good condition on the 8th day after an uneventful hospital course. The child was still asymptomatic when seen in the clinic 1 week later. At this time, 13 days after the onset of illness, the cold-hemagglutinin and streptococcus MG titers were negative.

The hospital course is shown in Figure 3.

COMPARISON BETWEEN CHLOROMYCETIN AND AUREOMYCIN IN THE TREATMENT OF PNEUMOCOCCAL PNEUMONIA

In view of the fact that the mode of management was essentially the same in cases of pneumococcal pneumonia treated with aureomycin or chloromycetin an attempt was made at the conclusion of the study to compare the efficacy of the two drugs in the disease.

There were 18 patients with pneumococcal pneumonia who received chloromycetin, and 11 who were given aureomycin orally. In both groups the age range, the duration of illness prior to the initiation of therapy and the severity of the illness were quite comparable (Table 3). On the average, the patients treated with chloromycetin received a larger dose approximating 25 mg. per kilogram of body weight per dose. The disparity was rather empirical since the optimal dose of both drugs for children has not as yet been conclusively worked out. The duration of therapy in both the aureomycin-treated and the chloromycetin-treated patients ranged between three and six days, with an average of five days.

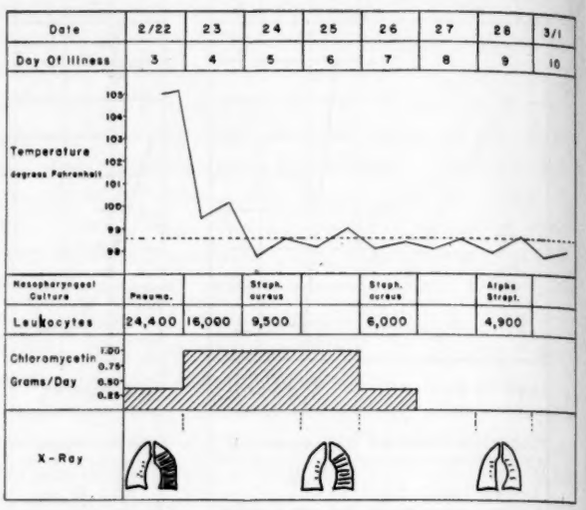

FIGURE 3. *Results of Chloromycetin Therapy in R. J.*

After initiation of therapy with both chloromycetin and aureomycin, a rapid defervescence ensued. In the patients treated with aureomycin the temperature returned to normal within twelve to forty-eight hours, with an average of twenty and two-tenths hours, whereas in those treated with

TABLE 3. *Comparison of the Therapeutic Efficacy of Aureomycin and That of Chloromycetin in Pneumococcal Pneumonia.*

DRUG	NO. OF PATIENTS	AVERAGE AGE	AVERAGE DURATION OF ILLNESS BEFORE TREATMENT	MAXIMUM TEMPERATURE	AVERAGE MAXIMUM WHITE-CELL COUNT	NO. OF PATIENTS WITH POSITIVE X-RAY FINDINGS	AVERAGE DOSAGE PER 24 HOURS	AVERAGE DURATION OF TREATMENT	AVERAGE DURATION OF FEVER AFTER START OF TREATMENT	NO. OF TREATMENT FAILURES
		yr.	*days*	*°F.*	*x10³*		*mg./kg. of body weight*	*days*	*hr.*	
Aureomycin ..	11	4.2	4.2	104.4	19.7	11	61	5	20.2	0
Chloromycetin .	18	3.2	3.6	104.0	21.2	18	124	5	23.0	0

chloromycetin, the duration of fever following institution of therapy ranged from twelve to sixty-four hours, with an average of twenty-three hours. This difference was not statistically significant. In regard to the rapidity of clearing of the nasopharyngeal culture of its pathogen, 61 per cent of the patients treated with aureomycin no longer showed pneumococci after five days and 70 per cent of those treated with chloromycetin were negative after a similar interval. In the aureomycin-treated group the time required for x-ray resolution ranged between four and seven days, with an average of five and nine-tenths days, whereas in the chloromycetin-treated series the range varied from three to twelve days, with an average of five and three-tenths days. In both groups the response to therapy was considered good in every patient and no failures were observed.

In view of the small number of cases treated in each group, only a few limited observations may be permitted from this comparative study. In the first place there did not seem to be any statistically significant difference in the response of patients with pneumococcal pneumonia to either aureomycin or chloromycetin since both drugs were extremely effective against this infection. No toxicity was observed when chloromycetin was employed except for a transitory leukopenia in several cases. On the other hand, the triad of nausea, vomiting and diarrhea was not infrequently encountered when aureomycin was used, and occasionally the drug had to be discontinued in view of the persistence of gastrointestinal irritation. As for a comparison between either of these two new antibiotics with sulfonamides or penicillin in the treatment of pneumococcal pneumonia, no categorical statement is possible at the present time in view of the limited number of cases treated.

Summary

Chloromycetin was used in the treatment of 33 cases of bacterial pneumonia in infants and children.

The therapeutic effect (based principally on the rapidity of return to normal of clinical, roentgenologic and laboratory findings) was considered favorable in all but 1 patient. In 32 of the 33 cases, the temperature was normal within three days of the initiation of the drug.

Chloromycetin may be regarded as an effective drug in the therapy of bacterial pneumonia.

We are indebted to Miss Sara Stevens, B.S., M.T., and Mrs. Susan Gouge for their technical assistance and to Miss Phyllis Allred, R.N., and Miss Lucie Knies, R.N., for their help in the compilation of statistics.

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RELIEF OF CHEST PAIN BY TETRAETHYLAMMONIUM CHLORIDE*

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THE intravenous administration of tetraethylammonium chloride to a patient acutely ill with thrombophlebitis and pulmonary infarction unexpectedly relieved the patient's severe pleuritic pain. As a result of this observation, the effect of tetraethylammonium administration has been studied in other patients with chest pain.

The present report concerns observations made on 35 male and 5 female patients with chest pain due to infarction, trauma, pneumonia, pleuritis, tuberculosis, neoplasm, mediastinal emphysema or myocardial infarction.

Tetraethylammonium chloride was given intravenously, each cubic centimeter of solution containing 100 mg. of the drug. Syringe injection was made slowly, while the blood pressure was being measured in the other arm; administration was suspended if the diastolic blood pressure fell, and was resumed as the pressure rose. Only in older and in debilitated patients was there usually a marked fall in blood pressure.

TABLE 1. *Effect of Tetraethylammonium Chloride on Chest Pain.*

CAUSE OF PAIN	NO. OF PATIENTS	SLIGHT OR MODERATE RELIEF	MARKED RELIEF
		NO. OF CASES	NO. OF CASES
Pulmonary infarction	8	2	6
Trauma	15	4	11
Pneumonia and pleuritis	8	4	4
Tuberculosis	5	4	1
Neoplasm	2	1	1
Mediastinal and cardiac disease	2	0	2
Totals	40	15	25

Originally, an effort was made to give each patient 3 or 4 cc. of solution (300 to 400 mg.). These amounts were well tolerated by young patients with acute illnesses, but in others the fall in blood pressure often permitted injection of only 2 or 3 cc. More recently, a smaller dose of 3 mg. per kilogram of body weight has been employed. No severe reactions have been encountered, and in no case has it been necessary to use neostigmine for control of circulatory collapse. Patients were kept in a recumbent position for thirty minutes after administration of the tetraethylammonium chloride, to avoid symptoms due to postural hypotension.

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RESULTS

In all cases a diminution of pain was noted. In some patients the effect was slight, being manifested chiefly by ability to breathe more deeply; in others the relief was considerable although brief in duration, but in the majority relief was marked and prolonged.

The results are summarized in Table 1. Included as having experienced marked relief are patients who were completely free of pain for at least an hour and a half or almost completely free for at least four hours; the majority of patients included in this group obtained relief for considerably longer periods, and in most cases the pain did not recur in its original intensity. The degree and duration of relief seemed to be influenced by the age of the patient as well as by the nature of the lesion responsible for the pain. Patients less than fifty years of age obtained satisfactory relief more often than older patients (Table 2), but relatively few older persons were treated because of reluctance to use this drug in patients with degenerative changes.

TABLE 2. *Effect of Tetraethylammonium Chloride on Chest Pain (Influence of Age).*

AGE	NO. OF PATIENTS	SLIGHT OR MODERATE RELIEF	MARKED RELIEF
		NO. OF CASES	NO. OF CASES
yr.			
Under 50	31	10	21
50 and over	9	5	4

Application of the chi-square test failed to demonstrate a significant difference between the results in the two age groups; this may have been due in part to the small number of older patients, and additional studies will be required before definite conclusions concerning the effect of age can be drawn.

Pulmonary Infarction

Eight patients with severe pleuritic pain due to pulmonary infarction were treated. In 5, aged twenty-four to fifty-four years, with pain unrelieved by morphine, the response to tetraethylammonium chloride administration was prompt, complete and prolonged. In another patient, aged fifty-five years, the relief of pain was marked but incomplete, whereas 2 patients, aged sixty-four and sixty-six,

remained in continued pain and discomfort although local tenderness over the thorax was diminished, and it was evident that deeper respirations were possible.

Traumatic Injuries

Four patients with pleuritic pain due to rib fractures were treated. Prompt and almost complete relief of pain for a six-hour period was obtained in an Army nurse, and similar relief of pain for an interval of five hours occurred in another woman with rib fractures incurred in an automobile accident. Two men, both alcoholic, experienced only slight and transient relief from tetraethylammonium chloride.

Striking results were noted in a group of 11 patients with severe pleuritic pain following diagnostic and therapeutic procedures. The pain followed aspiration biopsies of the liver in 8 patients; administration of 200-mg. doses of tetraethylammonium chloride gave prompt and impressive relief in all but 1. Severe pleuritic pain following a thoracentesis was completely relieved in 1 patient. Complete relief was obtained with only 150 mg. in a patient whose pleuritic pain developed after a therapeutic brachial-nerve block. Pleuritic pain occurring after a first-stage thoracoplasty in a patient with tuberculosis disappeared almost completely after a 300-mg. dose, but returned to its original intensity in forty-five minutes.

Pneumonia and Pleuritis

Six patients with moderately severe pain due to pneumonia were given tetraethylammonium chloride. The relief was complete and prolonged in 2 but was only partial in the others. Two patients who had severe pleuritic pain without roentgenologically demonstrable cause, presumably cases of pleuritis, were treated. Prompt and complete disappearance of pain was obtained. One patient noted a return of slight pain in twelve hours; the other patient experienced no recurrence.

Tuberculosis

Five tuberculous patients who had chest pain only on deep inspiration and cough were treated. The results were striking only in 1, although in the others the pain on respiration and cough was diminished for an average interval of four hours.

Neoplasm

Complete relief of severe pleuritic pain for an hour and a half was obtained in a patient with rib involvement by multiple myeloma, but only slight relief occurred in a patient with metastatic sarcoma.

Mediastinal and Cardiac Disease

A young woman with severe precordial pain due to spontaneous mediastinal emphysema obtained prompt, complete and permanent relief after administration of 125 mg. of tetraethylammonium chloride. A forty-two-year-old man with acute myocardial infarction whose precordial pain remained agonizing after 25 mg. (3/8 gr.) of morphine subcutaneously and 15 mg. (1/4 gr.) intravenously obtained immediate and permanent relief after injection of 300 mg. of tetraethylammonium chloride. Continuous electrocardiographic and careful clinical observation during and after administration of the drug revealed no untoward effects.

Comment

An action of tetraethylammonium chloride upon pleural and mediastinal pain apparently has not been previously reported. Lyons and his associates[1] noted dramatic relief of pain in 2 patients with acute myocardial infarction who were given tetraethylammonium chloride, but these investigators considered that the drug was contraindicated in the presence of coronary-artery disease. More recently, Shea and his co-workers[2] have reported the use of tetraethylammonium chloride for relief of cardiac pain in 16 patients with myocardial infarction or coronary insufficiency, and Christy[3] has studied intramuscular administration of this drug for the treatment of angina pectoris.

The pharmacologic and physiologic implications of these observations are of considerable interest. The action of tetraethylammonium chloride is not that of a general analgesic; during its action thoracic skin sensitivity to painful stimuli is not diminished.

Tetraethylammonium chloride is known to exert appreciable psychic side effects, and a psychogenic influence cannot be excluded in the patients who appeared to obtain slight or even moderate relief of chest pain after its use. It is unlikely, however, that the complete relief occurring in patients severely ill with definite organic lesions can be considered psychogenic, especially since in many cases injections of morphine and procaine had previously been ineffectual. In fact, the action of tetraethylammonium chloride was most striking in patients who manifested the least psychologic and physiologic disturbance.

The mode of action of tetraethylammonium chloride in relieving chest pain is uncertain. Capps[4] demonstrated that pain can be elicited by trauma to the parietal but not to the visceral pleura. The belief that pleural pain is due to irritation or inflammation of the parietal pleura and is carried through sensory fibers of the intercostal nerves has been questioned by Price,[5] who pointed out that intercostal-nerve blocks with procaine relieved pleuritic pain for much longer intervals than were attributable to the anesthetic action of procaine. Bennett and Latham[6] offered as an explanation the theory that the pain of pleurisy, like the pain of a sprained ankle, is due to muscle spasm, and postulated that a vicious circle was thereby initiated

so that temporary interruption of the chain by the anesthetic action of procaine resulted in a prolonged relief. Their observation that intravenous calcium administration and curare were effective in alleviating pleuritic pain supported this theory. If pleural pain were the result of intercostal muscular spasm, the effect of tetraethylammonium chloride might be due to its curare-like activity, which however, is exerted not by a curarizing action at the myoneural junction of skeletal muscles, but by a blocking effect at the ganglionic synapse.[7]

In addition to an action on a hypothetical muscle spasm it is necessary, to explain the relief of cardiac pain, to postulate, as Shea et al.[2] have done, an action upon coronary-artery spasm. This does not appear to be an adequate explanation for the effect of tetraethylammonium chloride upon pain due to acute myocardial infarction, and the possibility should be considered that the relief of chest pain by tetraethylammonium chloride is the result of a direct action on sensory pathways, interrupting afferent flow either at nerve ending, at synapse or centrally. Evidence suggesting a direct action upon sensory pathways has recently been provided by the observation of Sonnenschein, Jenny and Pfeiffer[8] that alterations in pain thresholds of the finger pads and nail beds are produced by administration of tetraethylammonium chloride.

The cardiovascular effects of tetraethylammonium chloride limit the application of the drug for relief of chest pain, especially in older patients. Tetraethylammonium chloride is a drug that must be used with caution in patients with hypertension or arteriosclerosis, and should not be used in patients with high diastolic pressures or impaired renal function. The alarming or fatal reactions reported have followed use of high dosages[9] or rapid administration,[10] although a profound reaction occurred in a young woman after injection of only 230 mg.[11] Serious reactions appear to be infrequent, however, when small doses are administered with care. Naide[12] has observed no severe reactions in the course of 1000 injections in ambulatory patients. He administered 200 mg. or less in patients under fifty years of age, but determined the dosage in patients over the age of fifty by response to a test injection of 50 mg.

Use of tetraethylammonium chloride should afford little danger to hospital patients free of advanced renal or cardiovascular disease when used at the rate of 3 mg. per kilogram of body weight. The value, especially in patients with pulmonary disease, of an analgesic agent that does not, like morphine, suppress cough and encourage atelectasis is evident. Tetraethylammonium chloride in low dosage provides a method of treatment worthy of trial in patients with severe chest pain not relieved by small doses of codeine or meperidine.

Summary

Tetraethylammonium chloride administered intravenously in relatively small dosage has been observed to relieve chest pain due to a variety of conditions, including pulmonary embolism, trauma, pneumonia, pleuritis, tuberculosis, neoplasm, mediastinal emphysema and myocardial infarction. Relief was notably complete and prolonged in patients with pain due to infarction and trauma. These results appear to justify a further trial of tetraethylammonium chloride for the treatment of severe chest pain.

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THEPHORIN OINTMENT IN PRURITIC DERMATOSES

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SINCE the report of Fourneau[1] and his French associates, there has been a widespread interest in the use of the so-called antihistaminics or histamine antagonists for diseases with an allergic background. Until quite recently, the antihistaminic drugs have been administered orally with good effect, especially in certain dermatoses such as the acute urticarias and urticarial drug reactions and some of the physical allergies.

The success achieved with the oral administration of the antihistaminic drugs in the allergic type of dermatoses led to their topical use in similar diseases. In 1947 Mayer[2] reported experimental evidence that the local application of 5 per cent triplennamine hydrochloride (Pyribenzamine) protected guinea pigs against epidermal sensitization to subsequent applications of paraphenyldiamine. Shortly thereafter, Feinberg and Bernstein[3] used 2 per cent Pyribenzamine ointment in 33 cases of atopic dermatitis and stated that 24 of these patients noted consistent relief from the use of the ointment. At the same time, Sulzburger and his associates[4] reported that the local use of Pyribenzamine cream was of distinct value only in lichen chronicus simplex and was of no value in atopic dermatitis.

In August, 1948, Woodridge and Joseph[5] reported the local use of 2-methyl-9-phenyltetrahydro-1-pyridindene (Thephorin) in disseminated neurodermatitis. They used a 5 per cent ointment of Thephorin in a carbowax vehicle. Of 23 cases of neurodermatitis disseminata, Woodridge and Joseph stated that 9 (39 per cent) showed 75 per cent or more clearing and 8 (35 per cent) showed 50 per cent clearing. Thus, approximately 74 per cent of these patients were much improved with Thephorin. However, most of them also took Thephorin orally.

Later in 1948, Shelmire[6] and Laymon and Schmid[7] reported the use of Thephorin locally in pruritic dermatoses. Shelmire stated that Thephorin ointment had good to excellent results in 55 per cent of his cases of atopic dermatitis, 75 per cent of lichen chronicus simplex and 60 per cent of miscellaneous pruritic dermatoses. Shelmire also noted a 1.3 per cent sensitization index in his series of cases and stated that Thephorin ointment was far superior to Pyribenzamine ointment in his experience.

In their series of cases, Laymon and Schmid found that Thephorin ointment had moderate to excellent results in 73.5 per cent of cases of circumscribed neurodermatitis. Their results in atopic dermatitis were as follows: excellent, 0; moderate, 55.5 per cent; and worse, 44.5 per cent. In their cases of miscellaneous pruritic dermatoses, they reported excellent results in 43 per cent and moderate improvement in 57 per cent of the cases.

PERSONAL EXPERIENCE WITH THEPHORIN OINTMENT

Because of the marked difference of opinion concerning the therapeutic value of the topical use of Thephorin ointment in so important a group of pruritic dermatoses, the study of the problem was undertaken. It was decided that, for a report of this nature to be of utmost value, the patients reported upon should be carefully followed over a period of months by the same observer. In this way, one could evaluate the results of the medication more exactly, and also determine whether any of the patients became resistant or sensitized to the topical remedy. All the patients were observed for a period before treatment with Thephorin ointment was instituted, to establish a definite diagnosis and to eliminate any cases that cleared up spontaneously.

In all, this report covers 74 cases. Of these, 24 were neurodermatitis disseminata, 26 were lichen chronicus simplex (neurodermatitis circumscripta) and 24 were miscellaneous dermatoses associated with pruritus. The group of neurodermatitis disseminata included typical cases of atopic dermatitis and allergic infantile eczema. The mis-

TABLE 1. *Results of Treatment with Thephorin Ointment.*

DIAGNOSIS	TOTAL NO. OF CASES	INITIAL RESULTS			SUBSEQUENT RESULTS*		
		GOOD TO EXCELLENT	SLIGHT TO FAIR	NO EFFECT	PATIENT WORSE	REFRACTORY CONDITION	SENSITIZATION
Neurodermatitis disseminata.....	24	0	8(33%)	10 (42%)	6 (25%)	6 (25%)	2 (8%)
Lichen chronicus simplex.....	26	10 (39%)	6 (22%)	10 (39%)	0	2 (8%)	0
Chronic dermatoses with pruritus	24	10 (42%)	2 (8%)	11 (50%)	0	4 (17%)	2 (8%)

*Improved patients.

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cellaneous group of chronic dermatoses associated with pruritus included typical cases of so-called nummular eczema. The results of treatment are shown in Table 1.

Discussion

Most of the cases of neurodermatitis disseminata did poorly with Thephorin ointment. Six of the 8 patients in whom there had been an initial slight to fair improvement subsequently became refractory to the ointment, and 2 of these patients became sensitized. A good percentage of the patients definitely became worse with the use of Thephorin ointment.

Thirty-nine per cent of the patients with lichen chronicus simplex were very much improved. Two (8 per cent) of these became refractory on continued use of the ointment.

Approximately half the miscellaneous group of chronic dermatoses associated with pruritus were improved with Thephorin ointment. Four (17 per cent) of these improved cases became refractory to the ointment, and 2 patients (8 per cent) became definitely sensitized.

Conclusions

Thephorin ointment is of very little use in neuro- dermatitis disseminata.

Thephorin ointment is of real therapeutic valu in lichen chronicus simplex (neurodermatitis circumscripta) and chronic dermatoses associated with pruritus.

About half the patients with initial improvement became refractory to continued use of the ointment.

Thephorin ointment has a sensitizing index of 16 per cent.

14 Maple Street

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THE USE OF WETTABLE DDT IN PEDICULOSIS

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MANY forms of therapy have been advocated for the control of the various types of infestation with pediculi. These have varied from the innocuous vinegar rinses to the more toxic derivatives of the benzene ring. Many of them are objectionable to the patient because of odor or difficulty of use. Not a few are severe skin sensitizers, and some are metabolic poisons.

With the advent of DDT, a new potent pediculicide was available and was used extensively as a powder by the armed forces. For the past two years, I have been using a "wettable DDT" in my practice with unprecedented success.

The wettable DDT that has been used is the type that is available through farm and seed stores and many gasoline stations. It is used by farmers, horticulturists, and others for the control of animal parasites of plant life. It is a fine, silky-smooth, white, fluffy powder, available in strength of 55 per cent active ingredient. When mixed with water, it forms, on agitation, a soapy emulsion that is very effective in the eradication of lice.

The patient is advised to wet the parts affected with water that is, the scalp hair in pediculosis capitis, the pubic and axillary hair in pediculosis pubis and the clothing in pediculosis corporis — and then to make a lather with the wettable DDT powder. The lather is allowed to stay on the parts for fifteen minutes and then is washed out with water. One such treatment will kill all lice, but will not affect the nits or ova that contain unhatched lice. Since the remaining nits will hatch into live lice within two weeks,† it is necessary to repeat this fifteen-minute treatment once weekly for three weeks. The second weekly treatment will kill all the lice that have hatched from the first day to the seventh day and the third weekly treatment will kill all that have hatched from the seventh to the fourteenth day. Since it takes a louse eleven to thirteen days to mature, and since a louse less than eleven days old is unable to copulate and lay eggs,† it is at once obvious that with this method of treatment, no nits will be laid down after the first treatment. Since nits hatch within fourteen days, it is evident that by the third treatment (the fourteenth day) all the eggs originally present will have hatched and no further lice will be produced from

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†Craig, C. F., and Faust, E. C. *Clinical Parasitology.* Fourth edition. 871 pp. Philadelphia:Lea & Febiger, 1945.

them by the end of the fourteenth day (third day of treatment).

Itching is relieved immediately after the first treatment (unless there is a dermatitis, pyogenic infection or scabies complicating the picture).

No dermatitis has resulted from this exposure to DDT, nor have there been any toxic metabolic manifestations. It is a simple procedure and is especially time and labor saving.

The following, a simple, large-scale scheme, will eradicate all lice from institutions, such as orphanages and hospitals for the care of patients with chronic disease, that are plagued by such infestations. All persons in the institution (including not only the inmates but all the personnel of the institution that are affected) are treated once weekly for three weeks. All new patients are given the same treatment for the first three weeks of their hospitalization. This eradicates the infestation and prevents any new patient from bringing in the disease again.

If wettable DDT is not available, a satisfactory substitute is a paste of equal parts of 55 per cent regular DDT powder with one of the newer synthetic shampoos or detergents, such as Drene, Halo, Vel and Phisoderm, or a powder from equal parts of regular DDT and Dreft, Swerl and so forth. This paste or powder is used in the same manner as the 55 per cent wettable powder.

Approximately, 15 gm. (1 tablespoonful) of wettable powder will be sufficient for the average male scalp and about 60 gm. (4 tablespoonfuls) for the average female scalp; 15 gm. is sufficient for each treatment of pediculosis pubis, and about 120 gm. for that of a tubful of clothing. In pediculosis corporis a single treatment of the clothing followed by ironing with a hot iron is sufficient to eradicate the disease.

It is important to treat all the infected members of the household at the same time.

Summary

Wettable DDT powder (55 per cent) is an effective remedy for pediculosis.

Its use is simple, clean and economical.

A method of therapy is presented for the eradication of lice in large institutions as well as in individual cases.

520 Commonwealth Avenue

MEDICAL PROGRESS

HEMORRHAGIC DISEASES (Concluded)*

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Clotting Time of Recalcified Plasma — "Recalcification Time"

Principle

If an optimal amount of calcium is added to oxalated plasma, containing an optimal number of platelets, coagulation results, and the time required for clotting has been termed the "recalcification time." Such a recalcification time depends on the concentrations of the various factors necessary for coagulation, including the blood platelet. In essence, it is a measurement of the coagulation time of plasma.

Method

A sample of 4.5 cc. of venous blood is mixed with 0.5 cc. of 0.1 molar solution of potassium oxalate. The blood is centrifuged§ at 1000 rpm for five minutes, and the plasma removed. Then, 0.1 cc. of this plasma is added to a 10 by 75 mm. test tube without a lip, and the tube is placed in a water bath at 37.5° C. To the plasma is added 0.2 cc. of 0.025-molar calcium chloride solution, a stop watch is started, and the contents are gently mixed. The tube is observed for coagulation at sixty seconds and every fifteen seconds thereafter, *the tube being kept in the water bath with as little agitation as possible.* The end point is complete coagulation of the plasma. The normal range of coagulation time with plasma centrifuged at 1000 rpm for five minutes is 90 to 120 seconds.[79]¶

Limitations and Interpretations

In general it can be said that any condition associated with prolongation of coagulation of whole blood is also associated with prolongation of the clotting time of recalcified plasma. Such prolonga-

*Adapted from *A Syllabus of Laboratory Examinations for Clinical Diagnosis* (in press) by permission of the Harvard University Press.

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§The platelet content of plasma centrifuged under these conditions is 350 to 800 x 10^3/mm.^{3}, an optimal number thus being insured when the platelet count of the whole blood is normal.

¶Note that the coagulation time of recalcified plasma is more rapid than that for whole blood; the mechanism of this is unknown.

tion is nonspecific and not indicative of any single disorder, and the interpretation of results is essentially the same as for the coagulation of whole blood. The primary point of difference between the coagulation time of recalcified plasma and the coagulation time of whole blood is the profound effect platelets have on the former and the slight effect on the latter when observed in glass tubes.

In severe *thrombocytopenia* the recalcification time is prolonged, such prolongation being directly proportional to the total number of blood platelets. The critical level of platelets at which prolongation occurs is about 100×10^3/mm.^{3} of *plasma* with the direct method of counting. This would correspond to a platelet count of 50 to 60×10^3/mm.^{3} of whole blood.* Thus, it is evident that the platelet count must be rather severely depressed before an alteration in recalcification time occurs. Prolongation of the recalcification time is also seen in hemophilia, *parahemophilia* (lack of "Factor V")[53] and *afibrinogenemia*. In *scurvy* and *thrombasthenia* the recalcification time is normal. Thus, it becomes evident that prolongation of the recalcification time may result from a deficiency of platelets and a deficiency of one or more of the factors of plasma necessary for coagulation.

Screening Tests for Abnormal Coagulation of Blood

Principle

When mixtures are made of whole unaltered venous blood from a patient and from a normal subject, the coagulation time may be used as a screening test to detect abnormalities of the clotting mechanism. For example, in coagulation defects resulting from a *deficiency of a plasma factor*, the addition of normal blood may restore the coagulation time toward normal. This may occur in conditions such as hemophilia, afibrinogenemia and deficiency of "prothrombin accelerator" substances. Conversely, in cases of *circulating anticoagulant*, the addition of the patient's blood to that of the normal subject will prolong the coagulation time of the normal blood, as in heparinemia and other conditions with circulating anticoagulants of undetermined nature.

Technically, mixtures may be made of samples of whole unaltered blood or of oxalated plasma with subsequent recalcification of the plasma. Because of the convenience of handling oxalated plasma, it is more frequently used.

Methods

Mixtures of whole blood. Two 10-cc. sterile syringes and needles are rinsed with sterile saline solution, and 3 cc. of sterile saline solution is then placed in each syringe. Simultaneous venipunctures are performed on the patient suspected of abnormal coagulation and on a normal subject. The saline solution† is then injected at the same time and same rate into each subject. A stop watch is started, and 10 cc. of venous blood is withdrawn from each subject at the same rate. Mixtures are then made of the blood of the patient and that of the normal subject by gentle transfer of samples to six saline-rinsed culture tubes without lips (13 by 100 mm.) in the amounts shown in Table 2.

In this system the coagulation times are determined for the whole bloods of both subjects as well as for mixtures.

Mixtures of oxalated plasma. Reagents. Potassium oxalate is used as an anticoagulant. One makes a 0.1-molar solution by dissolving 18.423 gm. of crystalline potassium oxalate ($K_2C_2O_4.H_20$) in 1000 cc. of distilled water. Then 1.0 cc. of this solution is used to prevent coagulation of 9.0 cc. of whole blood.

Calcium chloride, 0.025-molar solution, is made by dissolving of 2.77 gm. of calcium chloride (purified anhydrous) in 1000 cc. of distilled water.

Technic. A sample of 4.5 cc. of venous blood is obtained‡ from the patient and an equal sample from a normal subject; each sample is accurately added to 0.5 cc. of 0.1-molar solution of potassium oxalate and thoroughly mixed. The plasma is obtained by centrifugation of the oxalated whole blood at 1000 rpm for five minutes. Centrifugation is done simultaneously in the same centrifuge, thus ensuring the same speed of centrifugation for an

Table 2. *Preparation of Mixtures of Whole, Unaltered Venous Blood from a Patient with Hemorrhagic Disease and a Normal Subject for Observation of Plasma Defects or Anticoagulant Activity on the Clotting Time.*

Source of Blood	Volume of Blood in Tube					
	Tube No. 1	Tube No. 2	Tube No. 3	Tube No. 4	Tube No. 5	Tube No. 6
	cc.	cc.	cc.	cc.	cc.	cc.
Patient	2.0	1.6	1.2	0.8	0.4	0.0
Normal subject	0.0	0.4	0.8	1.2	1.6	2.0

Table 3. *Preparation of Mixtures of Oxalated Plasma from Patient and Normal Subject for Observation of Plasma Defects or Anticoagulant Activity on the Clotting Time.*

Source of Plasma	Volume of Plasma in Tube					
	Tube No. 1	Tube No. 2	Tube No. 3	Tube No. 4	Tube No. 5	Tube No. 6
	cc.	cc.	cc.	cc.	cc.	cc.
Patient	0.2	0.4	0.1	0.1	0.1	0.0
Normal subject	0.0	0.1	0.1	0.2	0.4	0.2

*When blood is centrifuged at 1000 rpm for five minutes, the platelets are concentrated in the plasma layer, being separated from the red cells.[17]

†This step permits each operator to synchronize his obtaining of a blood sample and serves to decrease contamination of blood by tissue juice.

‡There is no need to perform venipunctures simultaneously, and blood samples can be handled without hurry.

identical period for the two plasmas. The plasmas are mixed in a series of six dry culture tubes without lips (10 by 75 mm.) in the amounts shown in Table 3, and the contents of each tube is mixed by inversion. Then 0.1-cc. samples of each tube are transferred to separate dry culture tubes without lips (10 by 75 mm.), and the tubes are placed in a water bath at 37.5°C. The coagulation times of recalcified mixtures of plasma and of each subject's plasma are then determined in duplicate, as described above, by the addition of 0.2 cc. of 0.025-molar solution of calcium chloride.

Limitations and Interpretations

The technical limitations of these procedures are identical to those for the determination of the coagulation time. It is important to execute an immediately successful venipuncture on each subject so as to reduce to a minimum contamination of the blood with tissue juice. By the injection of 3 cc. of sterile saline solution contamination is further reduced. A small amount of tissue juice will grossly accelerate blood coagulation and obscure mild plasma defects or mild anticoagulant activity. When mixtures of oxalated plasma are used as a screening test for abnormal coagulation, it is essential that the speed and duration of centrifugation be identical for both samples, since marked reduction in the number of platelets will result in prolongation of the coagulation time of recalcified plasma.

In any condition in which there is a *deficiency* of one or more of the *plasma components* necessary for proper coagulation there is prolongation of the coagulation time. By addition of plasma factors to the abnormal blood, in the form of unaltered whole blood or plasma, the coagulation time of the abnormal blood is reduced toward normal. Thus, in such conditions as *hemophilia*, *fibrinogenopenia*, *afibrinogenemia*, *severe hypoprothrombinemia* and *parahemophilia*, the procedures outlined above will give normal coagulation times in all tubes except No. 1, in which the coagulation time will be variously prolonged depending on the severity of the plasma defect. In cases of deficiency of plasma factors the coagulation time of mixtures of whole blood or of mixtures of recalcified plasma will *not* be prolonged. Once a plasma defect is discovered, it becomes necessary to determine its nature more specifically; detailed methods are described by Owren.[19]

Abnormal coagulation as the result of *anticoagulant activity*, however, characteristically results in prolongation of the coagulation time of mixtures of whole blood and of recalcified plasma (prolonged in tubes No. 1 to 5 in Table 2 and 3). As the concentration of abnormal blood or of plasma is increased in the mixtures, greater prolongation of the coagulation time results. Once such anticoagulant activity is demonstrated, an attempt must be made to determine the type of anticoagulant that is present. This is done by diagnostic procedures involving the use of special reagents that are, as a rule, only available for research purposes. Therefore, reference should be made to the methods for determination of *antithrombin* and *antithromboplastin* as outlined by Quick.[1] *Hyperheparinemia* as a cause of abnormal coagulation has recently been shown to occur with *ionizing radiation*,[11] in *leukemia*[12] and in certain cases of *thrombocytopenia*.[12] The method of determining the degree of hyperheparinemia consists in adding a natural antiheparin (protamine sulfate) in increasing amounts to accurately heparinized venous blood and determining the amount of protamine required to reduce the coagulation time of the heparinized blood to normal. A normal control is always used for comparison (Allen et al.[12]).

By determination of the coagulation time of mixtures of whole blood or oxalated plasma, it is thus possible to differentiate plasma defects from circulating anticoagulants as cause of abnormal coagulation. Once such a distinction has been made it is necessary to carry out special procedures for the more specific identification of the defect or anticoagulant.

Determination of Prothrombin Activity

Principle

When optimal amounts of thromboplastin and calcium are added to citrated plasma, the factor measured is the speed of conversion of prothrombin to thrombin if other abnormalities* can be excluded. The time required for this conversion has been measured quantitatively as an arbitrary and biologic test in which the clotting time of the plasma becomes a measurement of its prothrombin activity. Measurement of prothrombin activity of plasma has become an important laboratory examination because it has important diagnostic and prognostic significance in diseases of the liver and in hemorrhagic diatheses and because the use of Dicumarol in the treatment of thromboembolic disease requires careful control of the prothrombin level, since death may occur from hemorrhage due to extreme hypoprothrombinemia.

Accordingly, the method of determining prothrombin activity in terms of its concentration in percentage of normal is of importance. *The method of Quick*[1] is a standard one-stage procedure and is described below in detail. Many modifications of this technic have evolved. One such modification, using dilution of the plasma with prothrombin-free plasma,[58] is known to give a high degree of accuracy and is also described below. The more complete two-stage method[62] is too demanding for clinical purposes; in essence, this method measures quantitatively the amount of thrombin formed from prothrombin.

*Rarely, there may be fibrinogenopenia or afibrinogenemia, deficiency of "prothrombin accelerators" or a circulating anticoagulant.

Quick Method

Reagents. A 0.1-molar solution of *sodium citrate* is used as an anticoagulant. It is made by dissolving of 29.412 gm. of sodium citrate ($Na_3C_6H_5O_7.2\ H_2O$) in 1000 cc. of distilled water; 1.0 cc. of this solution is used to prevent coagulation of 9.0 cc. of whole blood.

Thromboplastin is prepared by the addition of 4 cc. of a sterile solution of sodium chloride (0.85 gm. per 100 cc.) and 0.05 cc. of a solution of sodium oxalate (1.34 gm. per 100 cc.) to one ampoule (0.15 gm.) of lyophilized rabbit brain (Difco) that has been extracted with acetone. This mixture is incubated at 48°C. for ten minutes, with agitation every three minutes. Large particles of rabbit brain are then removed from the mixture by "filtration" through cotton: a small piece of cotton is loosely placed over the tip of a 20-cc. volumetric pipette, the cotton-covered tip of the pipette being immersed in the emulsion and gentle suction applied. *One should not centrifuge or filter through paper.**

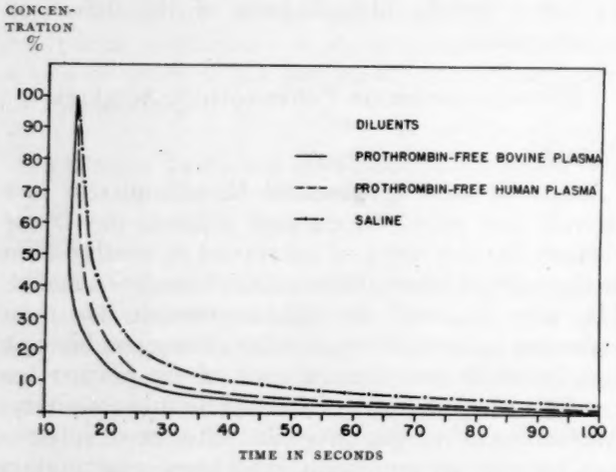

FIGURE 1. *Effect of Three Different Diluents of Normal Human Plasma on the Prothrombin Time in Seconds.*[48] *(The Method of Rosenfield and Tuft,*[58] *as Modified by Alexander and deVries,*[40] *Uses Prothrombin-Free Human as a Diluent; Frommeyer*[48] *Uses Prothrombin-Free Bovine Plasma.)*

When used as a chart for the conversion of prothrombin time (seconds) to prothrombin concentration (per cent), the activity of the thromboplastin must be determined by replotting of the curve whenever the thromboplastin is changed.

Thromboplastin as thus prepared is quite stable for many weeks if kept frozen (—20°C.) in 0.1-cc. aliquots in standard culture tubes (10 by 75 mm.) until ready for use. The potency of the thromboplastin is an essential element of the procedure and is standardized for each aliquot of material, as described below.

Calcium chloride, 0.025-molar solution, is made as described above under screening tests for abnormal coagulation.

Technic. All tubes and reagents are maintained at 37.5°C. in a water bath. To 0.1 cc. of thromboplastin solution in a standard culture tube with lip (10 by 75 mm.) 0.1 cc. of citrated plasma is accurately added. The tube is gently shaken to ensure mixing. With stop watch in hand, exactly 0.1 cc. of calcium chloride (0.025-molar) solution is added, and at the same instant the stop watch is started. The tube is held in the water bath, and the contents are gently mixed. A few seconds before clotting is anticipated, the tube is removed from the water bath, held in a horizontal position and moved gently back and forth. Clotting of the plasma is the end point; it is taken as occurring at the instant at which the plasma is no longer completely fluid. This procedure is repeated as a check, and the second determination should agree with the first within half a second to one second to be considered accurate. The prothrombin time is recorded in terms of seconds. With knowledge of the prothrombin time, it is possible, by means of a prothrombin-time-concentration curve (Fig. 1), to determine the value in terms of percentage of normal.

Determination of Prothrombin by Means of Dilution with Prothrombin-Free Plasma

The problems in determining prothrombin by the Quick method may be largely resolved by the use of a modification[40] of the method of Rosenfield and Tuft.[58]

Principle. The principles of the method are as follows: the prothrombin time is determined on a sample of citrated plasma by the usual method of Quick to estimate the activity of the sample, and the citrated plasma is then diluted with prothrombin-free normal plasma. Dilution with prothrombin-free plasma is necessary if the prothrombin time is relatively short, corresponding to a prothrombin concentration of 30 per cent or more. It is immediately apparent from inspection of Figure 1 that a difference of a few seconds in prothrombin time in this range of the curve is equivalent to large differences in the concentration of prothrombin. For example, in Figure 2 a prothrombin time of fourteen seconds corresponds to 30 per cent prothrombin, whereas thirteen seconds corresponds to an apparent concentration of 45 to 100 per cent. Manifestly, there are two technical limitations of this method that make it unsound: the concentration cannot be read accurately on the steep part of the curve; and small errors of estimating the end point may be greatly magnified when the time in seconds is converted to concentration. To remove these limitations, the plasma is diluted so that the prothrombin concentration of the mixture will be approximately 10 per cent of normal, as shown in Figure 2, thus permitting observation of the prothrombin time in part of the curve in which the deviation of a few seconds produces insignificant changes in apparent prothrombin concentration. *Dilution with saline solution cannot be recommended since all clotting factors are thereby diluted.*

*The thromboplastin solution is a milky-appearing emulsion. Removal of the small particulate matter will remove most of the thromboplastic activity.

Reagents. Thromboplastin and *calcium chloride* solution are prepared as described above. *Potassium oxalate* is used as an anticoagulant since oxalated plasma can be depleted of its prothrombin, whereas citrated plasma cannot. A 0.1-molar solution of potassium oxalate is made as described above under screening tests for abnormal coagulation; 1.0 cc. of this solution is used to prevent coagulation of 9.0 cc. of whole blood.

Adsorption of prothrombin. Prothrombin is readily adsorbed by the addition for each 1.0 cc. of oxalated plasma, of 100 mg. of powdered barium sulfate. The mixture is shaken, incubated for ten minutes at 37.5°C. with agitation every three minutes, and centrifuged at 3000 rpm for thirty minutes; the supernatant is poured off and put in the refrigerator at 4°C. until ready for use. *The prothrombin-free plasma should be used within 2 hours of its preparation and kept in the refrigerator during this period.* This disadvantage can be overcome by lyophilizing of large quantities of prothrombin-free normal plasma and reconstitution of this plasma with buffered distilled water immediately prior to use.[48] According to Owren[19] 50 per cent of "Factor V" is also removed by the barium sulfate adsorption of prothrombin, although the amount used is not stated. This can be obviated by the use of prothrombin-free ox plasma as the diluent, since it is rich in "prothrombin accelerators."

Preparation of time-concentration curve. In each laboratory a curve, such as that shown in Figure 1, must be prepared to determine the activity of the available thromboplastin for the conversion of prothrombin *time* to prothrombin *concentration* in *percentage.* The time-concentration curve is derived with prothrombin-free plasma, rather than physiologic saline solution, as the diluent of fresh normal plasma. The *principle* of the method is to collect and pool equal quantities of plasma from at least 5 to 10 normal subjects (preferably young males), 1 part of 0.1-molar solution of potassium oxalate being used for 9 parts of venous blood. A portion of the pooled plasma is treated with barium sulfate to remove prothrombin. With this prothrombin-free plasma as a diluent, the fresh pooled plasma is diluted serially to known *concentrations* of *fresh plasma* and the prothrombin time of each dilution determined as described below. From the known concentrations and times, a conversion curve is plotted as in Figure 1.

Technic of measuring prothrombin with prothrombin-free plasma. A sample of 4.5 cc. of venous blood is withdrawn and mixed with 0.5 cc. of 0.1-molar solution of *sodium citrate.* This blood is centrifuged and the plasma removed. The prothrombin time of the undiluted sample of plasma is determined, the method of Quick, as outlined above, being employed as the *first step.* If the prothrombin time is so short as to represent a prothrombin concentration of 20 to 30 per cent or more, the prothrombin concentration cannot be read accurately enough from the curve for proper reporting. The plasma is then diluted as described below.

As a *second step,* the plasma is *diluted* with prothrombin-free normal plasma so that the prothrombin concentration will be approximately 10 per cent of normal. The prothrombin *time* is then determined for the diluted sample, and the corresponding concentration in per cent is read from the curve; the concentration is then multiplied by the dilution factor and reported in terms of percentage.

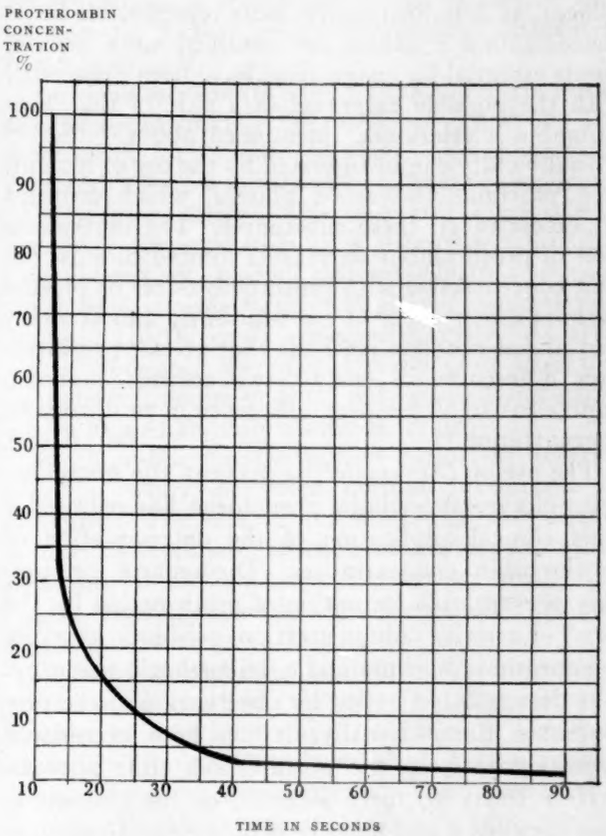

FIGURE 2. *Chart for Conversion of Prothrombin Time (seconds) to Prothrombin Concentration (Per Cent).*

The curve is made by dilution of a pool of fresh normal plasmas, prothrombin-free normal plasma being used as a diluent. This is the method of Rosenfield and Tuft,[58] as modified by Alexander and deVries.[40] The curve will vary with the activity of the thromboplastin and must be remade when the thromboplastin is changed.

As an example, the prothrombin time of an undiluted sample of plasma is 13 seconds, corresponding to concentrations of prothrombin of from 40 to 100 per cent. The plasma is diluted, — 1 part of fresh citrated plasma with 9 parts of prothrombin-free plasma, — and the prothrombin *time* determined. If the time is twenty-eight seconds, this corresponds on the curve to a prothrombin concentration of 10 per cent; this is multiplied by 10 to correct for dilution, giving a final value of 100 per cent for the concentration of prothrombin.

Limitations and Interpretations

Many of the time-concentration curves for prothrombin that are reported in the literature have been prepared from *saline* dilutions of plasma. Such dilutions diminish the amount of other factors necessary for coagulation and will show erroneously delayed prothrombin times, which may not be reliable or accurate in the determination of prothrombin concentrations in the range of 30 to 100 per cent of normal. If prothrombin-free plasma is used as a diluent, as described above, more reproducible time-concentration relations are obtained since all elements essential for coagulation have been preserved, with the possible exception of a part of the "prothrombin accelerators" mentioned above.[19, 46, 51, 56] This difficulty can be obviated by the use of lyophilized prothrombin-free ox plasma, which contains an excess of all these substances. The determination of prothrombin on plasma diluted to a 10 per cent concentration with prothrombin-free ox plasma permits a new order of *reproducibility* and *accuracy* and makes obsolete methods that attempt to interpret differences of one or two seconds that are equivalent to 50 per cent difference in prothrombin concentration.[58]

The use of *Dicoumarol* to prevent the complications of thromboembolic phenomena has required a wide clinical application of the determination of prothrombin concentration. Dicoumarol presumably prevents the formation of prothrombin by the liver. Excessive administration produces a severe hypoprothrombinemia and a hemorrhagic tendency. The dosage is controlled by observation of the prothrombin time. Usually, it has been considered necessary to keep the prothrombin time approximately thirty to forty seconds, or the concentration between 4 and 8 per cent of normal, to prevent thrombotic phenomena.

The prothrombin determination is of value in detecting the absence of prothrombin as a cause of hemorrhagic diathesis and in the study of response to vitamin K therapy.

In diagnosis the interpretation of the prothrombin time requires a knowledge of factors other than prothrombin deficiency that may cause prolongation, and a knowledge of the sources of error in the test. A prolonged prothrombin time by Quick's method is found in *afibrinogenemia* even though the prothrombin concentration may be entirely normal as determined by the dilution method using prothrombin-free plasma as a diluent. In addition, deficiencies of "prothrombin accelerators" result in prolongation of prothrombin time unless the dilution method using prothrombin-free plasma is employed. The prothrombin concentration is usually normal in the other hemorrhagic diseases as shown in Table 1.

Prothrombin Consumption

Principle

When unaltered normal venous blood is placed in a test tube, as in the determination of the coagulation time, clotting will normally occur within six to twelve minutes. When the clot is allowed to remain undisturbed for one hour after initial coagulation so as to ensure maximum coagulation, serum is expressed. The serum contains variable amounts of prothrombin, calcium, thrombin and serum "prothrombin accelerators," but *no fibrinogen*. Within two or three hours the thrombin present is converted to an inactive form, metathrombin. Various intervals are required for inactivation of the serum "prothrombin accelerators," but it appears likely from the available data that essentially complete inactivation occurs within twelve hours at a temperature of 37.5°C.[19, 60, 64] Such serum will then contain prothrombin and calcium. If this serum is added to a mixture of thromboplastin, fibrinogen and calcium, clotting will usually occur. The time required for clotting of this mixture becomes a function of the prothrombin that was not used (consumed) in the formation of the clot and that remains in the serum. Apparently, the prothrombin is the major variable in such a reaction mixture, and thus a prothrombin time and prothrombin concentration are obtained from the clotting time. The difference between the original plasma concentration time and the residual serum concentration of prothrombin is termed the "prothrombin consumption." The technic of the test is that used by Quick,[65] with the exception that prothrombin-free human plasma is used as a source of fibrinogen rather than prothrombin-free rabbit plasma.

Modified Quick Method for Prothrombin Consumption

Reagents. Thromboplastin and calcium chloride solution and *prothrombin-free human plasma* are prepared as described above.

Technic. Venous blood is allowed to coagulate according to the method described above. The clotting time is noted. One hour after initial coagulation the tubes are centrifuged at 800 rpm for five minutes; the serum is removed and kept at 37.5°C. for twenty-four hours.* A "prothrombin time" is determined as follows: to a mixture of exactly 0.1 cc. of thromboplastin, 0.1 cc. of prothrombin-free human plasma and 0.1 cc. of 0.025-molar solution of calcium chloride is quickly added 0.1 cc. of the unknown serum. A stop watch is started immediately upon addition of the serum to the mixture. The contents of the tube are shaken gently, and the instant the mixture is no longer *completely* fluid is taken as the end point. The prothrombin concentration can then be determined from the prothrom-

*Although serum is bacteriostatic, a sterile technic may be employed without increasing greatly the difficulty of the procedure.

bin time in seconds, as outlined above. This procedure is done at one, three and twenty-four hours after coagulation.

Limitations and Interpretations

The limitations of a one-stage method for measuring prothrombin time are the same as those described above. However, the difference in prothrombin consumption between the normal and abnormal is so large that these technical limitations are of secondary importance. The method for determination of prothrombin concentration described by Rosenfield and Tuft[58] may be used, however, if desired. Biologic limitations exist, in that serum contains active "prothrombin accelerators" that govern the speed of the coagulation reaction and therefore the prothrombin time. There still remains considerable doubt concerning exactly when these "accelerators" become inactivated in serum that is stored at 37.5°C. From the available literature[19, 60] the impression is gained that such inactivation is relatively rapid, there being little evidence of "prothrombin-accelerator" activity at the end of three hours of storage at room or water-bath (37.5°C.) temperatures. On the other hand, one investigator[64] reports 80 to 83 per cent activity after four hours of storage at 37.5°C. Because of the presence of active serum "prothrombin accelerators" as well as thrombin in the serum at one and three hours after coagulation, determinations of prothrombin concentration at these times are very difficult to evaluate. After a storage interval of twelve hours at 37°C., however, it is quite likely that the serum "prothrombin accelerators" are completely inactivated. By the use of prothrombin-free human plasma as a source of fibrinogen in the procedure, it is possible to maintain a relatively constant amount of available "prothrombin accelerators" in each reaction mixture after twelve hours of incubation of the serum.

By the procedure described, *normal* serum is found to have a residual prothrombin concentration of 10 to 20 per cent (80 to 90 per cent prothrombin consumption).

In *hemophilia* the serum has a prothrombin concentration of 80 to 100 per cent, and hence a low prothrombin consumption (0 to 20 per cent). Such a finding confirms the theory that in hemophilia prolonged coagulation is the result of improper formation of thrombin from prothrombin. That hemophilic blood ultimately coagulates is explained[65] on the basis that a small amount of prothrombin is eventually converted to thrombin over a prolonged period. Since thrombin is enzymatic in action, even a small amount is capable of converting fibrinogen to fibrin and thus resulting in superficial clotting as arbitrarily measured in glass tubes. The small amount of thrombin so formed will then slowly and continuously convert fibrinogen to fibrin until no fibrinogen remains in the serum. On the other hand, the *total* conversion of prothrombin to thrombin depends largely on the amount of active plasma thromboplastin and "prothrombin accelerators" present, the reaction between thromboplastin and prothrombin being, most likely, stoichiometric.[50] Thus, the lower the plasma thromboplastin concentration the smaller the amount of prothrombin that will be consumed or converted to thrombin in the process of coagulation. In *hemophilia* the plasma thromboplastin concentration is considered to be extremely low, whereas the "prothrombin accelerator" concentration is normal.[19]

In *thrombocytopenia* the prothrombin consumption is approximately 40 to 60 per cent.[64, 66] The mechanism for reduced prothrombin consumption may result from a reduction in a "platelet enzyme," as described above. This enzyme is considered necessary for activation of a precursor (thromboplastinogen) of plasma thromboplastin. Plasma thromboplastin, as mentioned above, converts prothrombin to thrombin stoichiometrically. As a result of decreased numbers of platelets or alteration in platelet function or both, only a small amount of active plasma thromboplastin is formed.

Prothrombin consumption is normal in *afibrinogenemia*, which indicates normal production of thrombin. The lack of coagulation in this disease is due to complete absence of fibrinogen, which thrombin would normally convert to fibrin, and is not concerned with any abnormality of prothrombin conversion.

In *parahemophilia* the conversion of prothrombin to thrombin has been shown to be slow owing to absence of an "accelerator substance." The total amount of prothrombin consumed in the process of clot formation, apparently, is of the degree of that seen in thrombocytopenia.[19] This is explained on the basis that the "prothrombin accelerators" may be concerned primarily with the *speed* of conversion of prothrombin to thrombin and are therefore indirectly concerned with the *total amount* of prothrombin converted or consumed in a given period.

Prothrombin consumption is normal in the remainder of the hemorrhagic diseases, as shown in Table 1. In the hemorrhagic diseases resulting from *circulating anticoagulants* and in *thrombasthenia* prothrombin consumption has not been reported.

It is evident, therefore, that the degree of prothrombin consumption depends on the presence of adequate amounts of plasma thromboplastin, platelet enzyme and "prothrombin accelerators."

Determination of Fibrinolysins

Normally, human plasma contains a balanced enzyme system consisting of the inactive precursor of a proteolytic enzyme, designated as profibrinolysin or plasminogen, and an antiproteolytic substance, designated as antifibrinolysin or antiplasmin. Under certain circumstances, the proenzyme be-

comes activated, resulting in the elaboration of the proteolytic enzyme, fibrinolysin or plasmin. The active enzyme received the name fibrinolysin from Dastre,[80] who found it to "destroy fibrin." Subsequent investigation has shown fibrinolysin to digest not only fibrin but also fibrinogen,[81] prothrombin[82] and, at least in one instance, a "prothrombin accelerator."[83] Because of the widespread alteration that can occur in the circulating blood and in clot formation, it becomes important to ascertain the presence or absence of this proteolytic enzyme as a cause of hemorrhagic diathesis. Since fibrinolysin (plasmin) is capable of digesting both fibrinogen and fibrin, it is evident that this enzyme can alter coagulation in any one of the following ways, depending upon its concentration: coagulation may be normal with subsequent *partial lysis* of the clot; coagulation may be normal with subsequent *complete lysis* of the clot; and there may be *no coagulation* because of rapid fibrinogenolysis and resultant afibrinogenemia.

Fibrinolytic activity is measured by observation of the stability of a clot of whole blood or of recalcified plasma. Further details are given in the excellent review by Macfarlane and Biggs.[67]

Method

Whole-blood technic. With sterile technic blood is obtained for determination of the coagulation time as outlined above, and the coagulation time is recorded. *It is important to watch closely for coagulation because fibrinolysis may be of such activity as to give the impression of incoagulability of the blood.* After coagulation has occurred the sample is maintained at 37.5°C. in a water bath and observed for dissolution of the clot at half an hour, one, two, three, four and twenty-four hours. Normally, the clot will remain intact and retain its content of red cells. If fibrinolysin is present the clot will be observed to decrease in size with loss of many of its red cells.

Plasma-saline technic. With sterile technic 0.2 cc. of citrated plasma is placed in a culture tube with lip (13 by 100 mm.), and 5 cc. of sterile saline solution added. To this mixture is added 0.2 cc. of thromboplastin and 0.2 cc. of calcium chloride (0.025-molar) solution, and the contents of the tube are mixed by inversion. Observations are made for lysis of this plasma clot as stated above. This method has advantage over the use of whole blood since the clot can be visualized more easily when the red cells are not present.

Limitations and Interpretations

Fibrinolysin occurs in severe burns and is possibly due to the presence of shock.[78] It has also been observed after surgical procedures as well as before them.[84] This observation led to the hypothesis that possibly the release of epinephrine during anxiety states operated as a mechanism for activation of profibrinolysin (plasminogen) normally found in plasma.[85] This hypothesis has since been tested, and it is possible to develop fibrinolytic activity in circulating blood upon the administration of epinephrine[85]; however, such activity does not develop upon the addition of epinephrine to whole blood in the test tube. Epinephrine release may be the mode of activation of the proteolytic enzyme that is frequently encountered in shock of all types. Since fibrinolysin digests fibrinogen, prothrombin, fibrin and possibly "prothrombin accelerators," there can be maintained, in shock, a vicious circle whereby fibrinolysin causes prolonged hemorrhage with further maintenance of shock and continued production of fibrinolytic activity. In any condition in which hemorrhage is unexplained the stability of the clot should be observed for the presence of fibrinolytic activity.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

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CASE 35451

PRESENTATION OF CASE

A sixteen-year-old schoolboy entered the hospital complaining of constipation.

Three months before entry while at a preparatory school the patient passed half a cupful of red blood one night, soiling his pajamas. A few days later he noted constipation, for which he saw the school nurse, who treated him with mineral oil and an enema. School closed shortly after this, and the patient went home. The constipation continued, and he frequently passed small amounts of semi-solid or liquid feces each day. At times he noted red blood on the toilet tissue and in the bowl. During the summer he worked as a caddie without undue fatigue. He lost 20 pounds, which was ascribed to a more active life and change in diet. For two weeks before entry he had anorexia and nausea in the morning. He also began to have frequent, small bowel movements at night and a dull discomfort in the rectum, which interfered with sleep. He was seen by a physician for a pre-school routine examination. Following this he was sent to the hospital.

The past and family histories were noncontributory.

Physical examination showed a healthy-appearing, well nourished boy. The only positive finding was a hard mass just inside the anus encircling the rectum. No definite ulceration was felt.

The urine was normal. The blood hemoglobin was 15.1 gm., and the white-cell count 10,000. The blood chemical findings were normal.

A barium enema showed partial obstruction in the rectum. Sigmoidoscopy was painful and therefore unsatisfactory, but some hard, red tissue was seen 2.5 cm. from the anus, from which a biopsy was taken.

DIFFERENTIAL DIAGNOSIS

DR. E. PARKER HAYDEN*: At first glance this case sounds as if it should be a clear-cut diagnostic problem, and it probably was a clear-cut problem for whoever was in attendance. The story, as far as bleeding is concerned, might suggest almost anything. Bleeding in a sixteen-year-old boy or girl is not common. The usual cause of bleeding in a person that age, in my experience, has been either polyp or fissure. This lad, however, had the symptoms of constipation, and as we read through the history it seems to be a progressive story, with bleeding becoming more frequent. The stools became more fluid, and there was some loss of weight, which I do not believe could be ascribed to the healthy summer occupation of caddying. The average boy would not lose 20 pounds, unless he was very fat, just from caddying in a healthy environment. The onset, two weeks before entry, of anorexia and nausea, together with increasing constipation, suggests a progressive ailment in the rectum. The statement that a definite hard mass was felt low down would suggest that the diagnosis ought not to be difficult, particularly with a biopsy, the result of which we do not have available in this report.

The first thing that one would think of from this description, despite the patient's youth, is a carcinoma of the lower rectum. Carcinoma can occur in a boy of sixteen. I have personally operated upon a boy of seventeen with carcinoma. We know that cancer does occur, usually in association with multiple polyposis, in a fair number of young people. The statement that no ulceration was felt would have to be taken with a grain of salt. One cannot always tell by palpation whether ulceration is present. With frequent movements and bleeding one would expect ulceration, and it probably was present. The normal hemoglobin is a little unusual with a cancer that has been present very long. On the other hand, that is entirely possible. The boy actually did have an annular mass — one that had grown all the way around the bowel wall. It would seem, therefore, that it must have been some sort of infiltrative lesion rather than a benign polyp. In inflammatory stricture there would, of course, be an annular ring, which could be due to tuberculosis or to lymphogranuloma inguinale.

If I were to hazard a guess on this case it would seem to me that carcinoma of the lower rectum was the obvious diagnosis to make on the basis of the résumé, but since it seems so obvious it is very likely something else. It also ran through my mind that he might have had an annular foreign body. A foreign body can produce ulceration, with blood and frequent bowel movements. I think ulcerative colitis can probably be excluded on the basis of the finding of the mass, although the sympto-

*Associate visiting surgeon, Massachusetts General Hospital.

matology of ulcerative colitis and that of cancer are often just about the same, and the latter can occur in the presence of the former.

There are other types of tumors that one sees occasionally in the colon, such as lymphosarcoma. If a sarcoma was present it might not be ulcerated, and one would not expect very much bleeding. I think the first diagnosis I would make, however, is carcinoma of the rectum, and if he had a carcinoma of the rectum it would most likely be based on multiple polyposis, although not necessarily so.

Are there any x-ray films available?

DR. JOSEPH HANELIN: These are films of the barium enema, apparently the only films made. The examiner was loath to put much barium into the bowel because after evacuation there was still a fair amount present, and he was afraid to get too great an accumulation above the lesion. There is clearly demonstrated in these films an annular constrictive lesion involving the rectum, beginning at the anus and going up for 5 or 6 cm. The appearance is quite characteristic of a malignant neoplasm. I would say undoubtedly that it is ulcerated.

DR. HAYDEN: On the basis of the x-ray report I certainly see no reason to change my first diagnosis. The description of the tissue biopsy would be consistent with carcinoma — a reddened and rather hard bit of tissue. Also the difficulty in proctoscopy is understandable from the degree of narrowing and its proximity to the anal canal, which is sensitive. I do not see how I can make any diagnosis but carcinoma of the rectum, which seems obvious in this case.

A PHYSICIAN: Would you consider lymphogranuloma inguinale?

DR. HAYDEN: That is a lesion in which one does not feel a true mass, although one might get that impression. Lymphogranuloma inguinale is simply an annular inflammatory condition going on long enough to produce scar tissue and gradual narrowing of the rectum. It may take the form of a short diaphragmatic stricture, 1.0 to 2.5 cm. above the anus, or may produce a tubular stricture.

DR. BENJAMIN CASTLEMAN: How often does one see rectal stricture in a male patient with lymphogranuloma inguinale?

DR. HAYDEN: Quite often. Dr. Earle Chapman and I gathered together a series of cases of lymphogranuloma inguinale in white people. As I recall it there was a predominance of males, although it has been stated in the literature that females predominate.

DR. CASTLEMAN: As far as stricture is concerned?

DR. HAYDEN: I was referring to the incidence of the disease in general.

DR. GORDON A. DONALDSON: Would tuberculosis give this sort of constricting lesion?

DR. HAYDEN: Tuberculosis of the lower rectum in a hyperplastic form is uncommon. I cannot accurately remember whether I have ever seen one. The disease usually takes the form of ulceration of the anus, whereas the hyperplastic form is encountered more often in the cecum, though it has been described in the rectum.

DR. THOMAS RISLEY: I saw this boy first in the office after he was sent in by his doctor. The feeling of the mass was not characteristic of carcinoma. It was extremely rubbery in consistence. It lay just inside the anal ring and on examination was painful. It was not possible to feel an ulceration or a crater. It felt as though the mass were completely covered by mucous membrane, and this was confirmed on introducing the sigmoidoscope. However, some tissue was removed and sent to the laboratory. On the day of operation we had not yet received the report from that tissue and because of the rubbery feeling we biopsied it again in the operating room and waited for a frozen section. On the basis of the frozen section we proceeded with a combined abdominoperineal excision of the rectum. There was a suggestion of lymphoma in the way the tissue felt.

CLINICAL DIAGNOSIS

Carcinoma of rectum.

DR. HAYDEN'S DIAGNOSIS

Carcinoma of rectum.

ANATOMICAL DIAGNOSIS

Colloid carcinoma of rectum, with metastases to regional lymph nodes in a sixteen-year-old boy.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The biopsy showed carcinoma. When we received the entire specimen, there was a large ulcerated tumor that looked like the garden-variety type of adenocarcinoma of the bowel. Microscopically, however, it was not the type of adenocarcinoma that we see ordinarily with well formed glands but a signet-ring-cell type of colloid carcinoma, a type that is more often seen in the stomach. The cytoplasm of each cell was replaced by mucoid material pushing the nucleus to one side to form what is known as a signet-ring cell. This type of tumor is usually a very malignant one. In this particular case the tumor had extended anteriorly to involve the serosa. Sixteen out of seventeen lymph nodes examined were involved.

We had some years ago, I believe, a carcinoma of the bowel, also colloid in type, in a child of seven or eight years. That child came in to the hospital because of a mass in the groin, and on biopsy it proved to be a metastatic lymph node full of colloid carcinoma. The primary site was found in the rectum.

DR. HANELIN: Was any calcification found?

DR. CASTLEMAN: I do not believe so.

DR. HANELIN: The reason I ask this question is that I am thinking of a similar case in which extensive calcification was demonstrated in the x-ray films.

CASE 35452

PRESENTATION OF CASE

A seventy-three-year-old housewife was admitted to the hospital because of abdominal pain.

Approximately two and a half weeks previous to admission the patient had a sudden onset of severe substernal pain radiating through to the back and associated with dyspnea but no sweating or pallor. She was agitated and in acute discomfort for several hours. For two days following this episode of pain she remained in bed, and the only complaint was nausea with several attacks of vomiting. On the third day after this episode an electrocardiogram showed a small Q wave and inverted T wave in Lead 1, with changes in one of the chest leads suggestive of "a small posterior infarct." After ten days of bed rest she became active again and seemed well. Twenty-four hours before admission, following her lunch, she felt somewhat nauseated. An hour or so later she had a sudden onset of persistent vomiting and retching, followed in a short time by urgent watery diarrhea. She gradually developed severe abdominal pain. This was not relieved by morphine administered by a physician, but the nausea and diarrhea subsided somewhat. Several hours before admission the temperature was 102°F. Examination by a physician disclosed a blood pressure of 140 systolic, (?) diastolic, rales at both bases and a diffusely tender abdomen. She was sent to the hospital. During this time she developed a feeling in the left leg as though "her leg had gone to sleep."

Five years before admission the patient had an attack of substernal pressure, pain in both upper arms and dyspnea. She had been seen by a physician, who diagnosed the condition as myocardial infarct. After several weeks of bed rest she resumed activity and was asymptomatic until the present episode.

Physical examination revealed a dehydrated, febrile, seriously ill woman. The thyroid gland was bean-sized and hard. The heart was enlarged 12 cm. to the left in the fifth intercostal space. The sounds were of poor quality. There were fine sticky rales throughout the entire right chest up to the midscapula anteriorly and posteriorly on the left, with diminished breath sounds at both bases. The left leg was cool from the hip to the knee and cold from the knee down; it was mottled with bluish discoloration. The left femoral pulse was not palpable. There was some pallor and a greenish tint to the toes. There was moderate abdominal spasm throughout. Peristalsis was diminished and somewhat high-pitched.

The temperature was 102°F., the pulse 110, and the respirations 18. The blood pressure was 90 systolic, 70 diastolic.

Examination of the blood showed a hemoglobin of 14 gm. and a white-cell count of 18,500. The urine had a specific gravity of 1.020 and gave a ++ test for albumin. The sediment contained frequent granular casts, rare red cells and 10 white cells per high-power field. An electrocardiogram was interpreted as showing slight tachycardia and abnormal T and S waves that could be due to coronary disease or to the combined effects of coronary disease and high blood pressure or aortic-valve disease. The T waves were unusually wide, and the QT interval was long. An electrolyte imbalance was suggested.

The patient was given digitalis, and fluid was administered by clysis. Attempts at deflation with a Miller–Abbott tube were unsuccessful. On the third hospital day the blood chloride was 90 milliequiv. per liter, the nonprotein nitrogen 64 mg., and the total protein 5.8 gm. per 100 cc. The temperature showed a definite upward trend. On the fourth hospital day it was noted that the right femoral artery also was not palpable. The abdomen was distended and had a doughy feel, but peristalsis was audible.

The patient gradually became comatose and died on the sixth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. JOHN T. QUINBY*: This clinical history is that of a seventy-three-year-old woman with a fatal illness of two and a half weeks' duration. It seems to me that most of the features of this case may be accounted for by a dissecting aneurysm of the aorta, with a number of sequelae that follow very logically from this not too uncommon lesion.

To recapitulate briefly, this woman had, five years before admission, an episode of substernal pressure and dyspnea considered by a physician to have represented a myocardial infarct. I see no reason to doubt that diagnosis. One notes that there was associated pain in both upper arms. Her terminal illness began with severe substernal pain, sudden in onset, with radiation through to the back and dyspnea. This time pain was not experienced in the arms. About two weeks later, she experienced, with fairly sudden onset, an acute and severe abdominal disorder. It was characterized by persistent vomiting and retching followed by urgent watery diarrhea and severe abdominal pain, and a day later a maximum temperature of 102°F. The abdomen showed "moderate spasm throughout"; peristalsis was diminished and somewhat high-pitched. Rather rapid pulse and falling blood pressure, to near-shock levels, were noted, though it does not seem from the history that frank clinical shock — that is, peripheral vascular collapse — ex-

*Assistant in medicine, Massachusetts General Hospital.

isted. Three days later the abdomen is described as distended and as having a doughy feel, with peristalsis still audible. A guaiac test on the material passed by rectum is not mentioned. A positive guaiac test here would be of interest, and would tend to confirm the impression I get of this acute and progressive abdominal accident — namely, that it represented mesenteric-vessel thrombosis, with infarction, probably extensive, of the bowel. Coming right on the heels of this process occurred another (an arterial) occlusion first in the left leg, going on to gangrene, and later in the right, without the development of gangrene.

This sequence of events could be well accounted for by a dissecting aneurysm of the aorta, beginning either in the ascending or the thoracic portion and extending farther and farther down to include eventually both common iliac arteries in the same morbid process — namely, the creation of an artificial cleavage plane in the media, first of the aorta, then of any of its branches to which the dissection extends, with resulting marked narrowing of the true lumen and diminution or complete cutting off of the blood flow in the involved vessels. Such a process could also account for occlusion of one or both mesenteric arteries.

The diagnostic problem in cases of this sort is to differentiate dissecting aneurysm of the aorta and coronary thrombosis, with myocardial infarction. In my opinion the first is the better diagnosis. I think so for several reasons: first, because almost every fact in the clinical history is consistent with such a diagnosis; and secondly, because the sequence of arterial occlusions seems better explained this way. As far as my knowledge goes, the successive occlusion of two major aortic branches (three, counting both iliacs) is a very rare event as a sequel to thrombosis on the endocardium, whereas it is very common with dissecting aneurysm. I think that if a very large myocardial infarct were the source of emboli from the heart, the probability of two successive arterial embolizations, both at their origins from the aorta, would be very small. Furthermore, one would have to postulate extensive myocardial damage, I think (in the absence of auricular fibrillation), and here the chances would be that endocardial thrombi would not be limited to the left side of the heart; we have no data on which to base a diagnosis of pulmonary embolism, it seems to me. Finally, I think that the location of the patient's pain is more characteristic of dissecting aneurysm than of coronary thrombosis. Also, with a myocardial infarction severe enough to cause this whole picture, the characteristic electrocardiographic pattern should be seen, and it was not present here. For these reasons, I prefer the first diagnosis. The strongest objection to it is the apparent presence of congestive failure. We are led to think of a recent, severe myocardial accident to help explain it, since there is no evidence that failure existed prior to the present illness. As I shall indicate later, however, I think it can be accounted for without this supposition. A third possibility is that the aortic dissection proceeded also in a retrograde direction, to involve the mouth of at least one coronary artery. This not uncommon sequel may have been present here. I see no way of knowing, but I doubt a large, recent myocardial infarction, and I think that in any case the occlusive sequelae were in all probability due to dissecting aneurysm of the aorta.

To discuss certain details of the history in the light of a diagnosis of dissecting aneurysm of the aorta, let us consider first the question of the immediate cause of death. With this aortic lesion the terminal event is usually rupture of the aneurysm. This is found to occur into the pericardial sac, with cardiac tamponade, into the mediastinum, frequently with hoarseness, into one or both pleural cavities, and into the peritoneal cavity, in about that order of frequency. In this case, however, there is little in the clinical history to indicate such an event. Death, I believe, was due to bowel infarction, with obstruction, distention, dehydration, azotemia and the presence of congestive failure. Very likely, some peritonitis was present.

Of course an acute abdominal episode of this type with bowel infarction is often precipitated by strangulation of the bowel, as in hernia or volvulus, or by infection in an abdominal organ tributary to the portal vein, as in appendicitis or pelvic infection. In such cases thrombosis usually involves the mesenteric veins. In this patient, I believe mesenteric arterial occlusion, probably with thrombosis, is more likely, fitting in with the initial aortic lesion that I have postulated. One or both mesenteric arteries may be involved; if one alone, the superior mesenteric is the more apt to lead to infarction, because of the freer anastomosis

that occurs between the end vessels of the systemic arteries and the inferior mesenteric branches.

The basal rales, extending on the left halfway up the chest, in addition to the suggestion of bilateral pleural fluid and the finding of definite cardiac enlargement, point to congestive failure. This, I think, can be explained without postulating a further coronary occlusion in the present illness. I think the patient must have had hypertension. In the reported cases of dissecting aneurysm of the aorta this has been an invariable finding. We also are assuming that five years before this episode she suffered a myocardial infarction. The fact that no blood-pressure reading over 140 systolic is recorded during her hospital stay almost certainly is a reflection of the profound prostration going with intestinal infarction and obstruction. Thus, I think heart damage by coronary-artery disease and by hypertension manifested itself before the present illness. If tachycardia, fever and azotemia, possibly with increased serum potassium level, are added to this, cardiac decompensation is understandable. If further coronary occlusion did occur, the most likely mechanism would be a progression of the dissecting aneurysm in a retrograde fashion, as mentioned eralier.

The urinary findings are a good specific gravity of 1.020, a ++ test for albuminuria and frequent granular casts, rare red cells and 10 white cells per high-power field in the sediment. The serum nonprotein nitrogen was 64 mg. per 100 cc. Except for the 10 white cells per high-power field in the sediment, there is nothing not entirely compatible with congestive failure and dehydration. Vascular nephritis of more than minimal degree I should doubt to have been present, with a good concentrating power. The moderate azotemia should be classed as prerenal, I think, and the pyuria — if the leukocytes came from the bladder — could reflect the low-grade cystitis that is almost the rule in elderly women.

The fact that renal function was fairly well preserved does not throw out the diagnosis of dissecting aneurysm of the aorta. Frequently, the renal arteries are not involved, though the dissection extends distal to them, and in other cases when they are involved, renal function has not appeared greatly impaired. The exact anatomical explanation for this is beyond my knowledge to discuss.

The description of the thyroid gland as bean-sized and hard is difficult to interpret. I cannot see that the clinical history points to thyroid disease of any type. It would seem that the gland was perhaps smaller than normal and harder than normal. An adenoma may have been present, or perhaps this was an involuted gland in an elderly person.

The low serum protein of 5.8 gm. per 100 cc. is consistent with the patient's nutritional defect, combined with her age. The blood chloride value of 90 milliequiv. per liter is somewhat below the normal range of 98 to 103 milliequiv. and is consistent with the loss of chloride through vomiting and diarrhea. The white-cell count of 18,500 is characteristic of mesenteric thrombosis and bowel infarction.

Electrocardiographic studies in this patient are certainly consistent with the diagnosis of dissecting aneurysm. In this condition the reported findings have been left-axis deviation usually, and a definite pattern of left ventricular strain in a majority of cases. A few cases have shown additional changes suggesting the presence of coronary-artery disease. None of the reported tracings could be considered entirely normal, and yet changes definitely suggestive of an acute myocardial infarct have not been seen, even in cases in which the coronary arteries themselves were involved in the dissection.

The findings in our patient appear to fit well with this experience. The changes in the T waves in Lead 1 and 2 noted on the third day of illness are consistent. Later the tracing showed, besides some tachycardia, abnormal T and S waves, with widening of the T waves and prolongation of the QT interval. An electrolyte imbalance was suggested, as well as an interpretation to the effect that the pattern suggested coronary-artery disease with left ventricular strain. Certainly, some electrolyte disturbance existed, and if with the patient's azotemia there was associated a significant elevation of serum potassium, the widened T waves and increased QT interval may have been due to that. Also, I believe, some coronary-artery disease was present before the onset of the last illness.

Clinical Diagnoses

Acute myocardial infarction.
Embolism to mesenteric artery.
Embolism to femoral artery, bilateral.
Acute pulmonary edema.
Congestive failure.

Dr. Quinby's Diagnoses

Dissecting aneurysm of aorta.
Occlusion and thrombosis of mesenteric arteries, one or both.
Infarction and gangrene of bowel, probably both small and large intestine.
Peritonitis?
Occlusion of left common iliac artery, total.
Occlusion of right common iliac artery, incomplete.
Gangrene of left leg and foot.
Generalized arteriosclerosis.
Arteriosclerotic and hypertensive heart disease, with old coronary thrombosis and myocardial infarction, and ? recent coronary occlusion.
Adenoma of thyroid gland?
Pulmonary edema.
Hydrothorax, bilateral.

Anatomical Diagnoses

Coronary thrombosis, recent, left anterior descending branch.
Myocardial infarction, left ventricle, recent, with mural thrombus.
Embolization, multiple, of superior mesenteric and femoral arteries.
Gangrene of ileum.
Peritonitis, purulent, generalized.
Bronchopneumonia, lower lobes of lung.
Arteriosclerosis, generalized.
Nontoxic nodular goiter.

Pathological Discussion

Dr. David G. Freiman: Upon opening the abdomen we noted that the omentum, loops of small bowel and portions of the large bowel were matted together by a thick yellow exudate, and a small amount of gray, murky fluid lay free in the pelvis. The jejunum and proximal third of the ileum were moderately dilated and congested. Beyond this point the ileum became gradually less distended, pale and friable, and a few scattered patches appeared dark and necrotic. The lowermost portion of the ileum and the large bowel, though flabby, showed no obvious gangrene. The cause of the gangrene in the small bowel was a reddish-gray, adherent embolus in the superior mesenteric artery, which extended from the point of origin of the ileocolic artery distally for a distance of about 2 cm. Both inferior and superior mesenteric veins contained adherent laminated thrombi extending distally into the smaller tributaries. These were undoubtedly secondary to the intestinal necrosis. Emboli were also present in both femoral arteries extending distally from the level of the inguinal ligaments. That on the right was slightly adherent and encroached upon the profunda branch. Both arteries below the points of occlusion showed severe sclerosis to the point of marked narrowing, but the lumens were patent. Thus, practically all Dr. Quinby's diagnoses relating to the abdomen were confirmed. The arterial occlusions were due, however, not to an aortic dissection but to an unusual multiple embolization, a source for which was found in the heart. A recent myocardial infarction involved the anterior apical and part of the adjacent lateral walls of the left ventricle, and a mural thrombus about 3.5 cm. in diameter was adherent to the endocardium in the region of the apex. About 1.5 cm. below the point of origin of the descending branch of the left coronary artery, a recent occlusion was present. The left circumflex and right coronary arteries were sclerotic to the point of marked narrowing in several areas, but were not occluded. The lungs showed marked congestion in the posterior and inferior portions of the lower lobes, and microscopical examination revealed bronchopneumonia in these areas. There was no pleural fluid. The thyroid gland contained several small cystic nodules.

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MEDICAL EDUCATION AT MESA VERDE

ONE of the pictorial magazines recently presented a photograph of the governors of Utah, Colorado, Arizona and New Mexico, seated at a table placed over the exact spot where the boundaries of these four states meet. It would be of interest to know what they had to say to each other, if anything, about medical education.

The ratios of the 1949 freshman medical students to the populations for these four states swing from the very highest to the very lowest in the United States. The ratios for all the states are shown in the September 3 issue of the *Journal of the American Medical Association*. Utah is the highest, with 10.5; New Mexico is the lowest, with 1.5; Colorado and Arizona are 7.6 and 3.1 respectively. Or one might similarly arrange a luncheon table at the point where the boundaries of Wyoming, South Dakota and Nebraska converge, the ratios for these three states being 2.6, 6.6 and 8.9.

In the same number of the *Journal* it was editorially suggested that these discrepancies had been noted in Washington, and it was pointed out that the bill for federal aid to medical schools now pending before the Senate provides, "No payments may be made to any school unless such school has filed an application therefor. . .which contains adequate assurance, as determined by the Surgeon General that such school provides and will provide reasonable opportunity for the admission of out-of-state students." Under date of September 2 the American Medical Association also released a statement to the press under the caption "Residency Limitations by Medical Schools Held to be Disservice." In this statement it is pointed out that although tax-supported institutions might be expected to render their major services to the community that supports them, the exclusion of all nonresident students may not prove to be in the best interest of the community or the region of which the community is a part.

When the ratios quoted above are plotted geographically, it is plain that it is a regional problem, and could be more satisfactorily met by regional arrangements than if every medical school were prevailed upon to open wide its doors to all comers. At least it seems appropriate for a substantial majority of the medical students in the United States to be able to receive their professional training within a reasonable distance of their places of residence. There may be good reasons why certain persons want to cross the continent for purposes of study, and there may be good reasons for certain schools to want their students to be gathered from widely dispersed areas, but it is hard to believe that any state has five times as many qualified candidates as its next door neighbor. It is probable that the admission authorities of the medical schools are sensitive to and sympathetic with their regional needs, but the ultimate authority of tax-supported institutions may rest in governmental bodies. Regional consciousness is a difficult thing for politicians to acquire, particularly at what is known as the "state level." More dinners, or card games, or whatever it is that governors do when they meet at Mesa Verde might prepare them to carry back to their legislatures a far-sighted

point of view toward their whole region as well as their individual states. This kind of leadership would help.

In the meantime probably every medical school in the country would be doing itself a good turn if it were to encourage application from residents of the states with the lowest ratios of medical students to populations.

PEACETIME USO

Mr. Karl K. Van Meter, executive vice-president of the United Service Organizations, consisting the YMCA, National Jewish Welfare Board, Salvation Army, National Catholic Community Service, YWCA and National Travelers Aid Association, points out the need for reactivating the USO now, in peacetime, and urges that funds be raised privately or through the agency of local community chests for this purpose.

With the present armed forces numbering over one and one-half millions, 70 per cent or more below the age of twenty-one, the desirability of some sort of benevolent civilian influence is evident, perhaps to an even greater extent than in wartime. Then the nearness of actual danger furnished incentive enough to serve. Military service in time of peace, however, directed as it is to warding off a more distant danger, leaves the individual service-man's incentive to be largely derived from the appreciative attitude of the public with whom he comes in contact. The responsibility of strengthening the armed forces has been rightly accepted, and with it goes the responsibility for their spiritual and social welfare.

It may be asked why this job should be done by volunteer workers on privately raised funds (the goal is twelve million dollars) rather than being included in the military budget, of which it would be an infinitesimal fraction, and it will come as a surprise to those who associate President Truman's name with the "Welfare State" to learn that a letter urging the former method appears in Mr. Van Meter's brochure over the signature of Harry Truman himself. Regardless of how efficient the military establishment has been, is now or may become, experience and common sense show that the part of a soldier's morale that depends on his contact with his civilian background and surroundings cannot be supplied by military officialdom. The nation wants its sons efficiently trained and disciplined for national defense, but during their training at home or abroad it wants them "in contact with the normal and wholesome activities of civilian life" so they will not return "bitter and disillusioned, resentful of the treatment they have received from civilians." Furthermore, "much of USO activity is of a religious and spiritual nature which no governmental auspices could appropriately provide."

Mr. Van Meter makes out so unanswerable a case for reactivating the USO now, four years after the ending of the war, that one cannot help wondering why so little has been done about it before.

POLIOMYELITIS GOES UNDERGROUND?

The virus of poliomyelitis, according to a hypothesis recently advanced by L. E. Rector,* of St. Louis, may quite literally go underground. This hypothesis is based on the assumption that any single host or vector of poliomyelitis must fulfill certain criteria. It must be found throughout both the temperate and tropical zones; it must account for the frequently observed tendency of the disease to begin and to have a higher incidence in rural than in urban communities; it must account for the seasonal tendency of the disease in man; and it must be so inconspicuous as to have escaped consideration to date.

The ground mole, happy hero of all the creatures that people the damp and sunless habitations found in Kenneth Grahame's *The Wind in the Willows*, fulfills these requirements. Voracious, ever on the forage, the mole adapts the level of his burrowing to that of his natural quarry, the earthworm. In the winter his runs are deep in the earth, in the summer so shallow as barely to be covered by the roots of the overlying vegetation. If a true representative of the grass roots is wanted, it will be the mole. Persons lying on the ground in the summer, whether in park or pasture, may be cultivating the acquaintance of the mole to a degree that invites even the transfer of a virus.

*Rector, L. E. Mole as possible reservoir of poliomyelitis. *Arch. Path.* 47:366-377, 1949.

Because of the hypothetical possibility that the mole might be the host of poliomyelitis, moles from Forest Park, St. Louis, were made the subjects of an investigation into their susceptibility to the virus. A number having been injected intracerebrally with filtrates of infected mouse brains or with stool filtrates from child victims of the disease were kept under observation.

Various clinical signs were recorded, including anorexia, cardiac arrhythmias consisting of dropped beats and extrasystoles, and coming to the surface to die — an unnatural procedure for moles. At autopsy no lesions typical of poliomyelitis were found, but this lack of pathology is found also in rabbits subjected to inoculation with the virus.

In the unremitting search for the method of spread of infantile paralysis, each possibility must be explored. There is as yet no proof that the mole carries the virus of the disease, but there is also no proof that it does not.

RETIREMENT OF DR. FAXON

THE Massachusetts General Hospital's traditional "Ether Day" celebration was made this year the occasion for an inspired farewell party to the retiring director, Dr. Nathaniel Wales Faxon. Dr. Faxon's eminence as one of the country's leading hospital directors was emphasized by various speakers, and the fact was not lost sight of that he had begun his career as a country doctor in Stoughton, Massachusetts.

This breadth of experience is enough in itself to make the *Journal*, in wishing him a happy "retirement," hope that it will not be too retired. His services to the community as an elder statesman will be so valuable that he will, no doubt, not be permitted to become bored with idleness between his fishing trips.

Important advances are daily made in the dental art. Colleges, based upon the best and most thorough principles, are springing up in various sections of the States. Indeed, the progress of this science here is attracting much attention in England and on the Continent of Europe; and amongst those things in which we can boast a pre-eminence over the old world, may be safely enumerated dental surgeons.

Boston M. & S. J., *November 7, 1849*

NOTES FROM THE MEDICAL EXAMINER

USE OF BLOOD GROUPS IN CASES OF DISPUTED PATERNITY

The application of blood groups in cases of disputed paternity depends upon the fact that the laws of their inheritance are accurately known. Thus, neither antigen A nor antigen B will appear in the blood of a child unless it was present in the blood of at least one of the child's parents. In addition, 2 persons of Group O will never produce a child of Group AB. Conversely, 2 persons of Group AB will never produce a child of Group O. Table 1 shows the possible outcome of the various types of mating.

TABLE 1. *Combinations Allowing an Alleged Father to Establish Nonpaternity.**

PUTATIVE FATHER BLOOD GROUP	KNOWN MOTHER BLOOD GROUP	KNOWN CHILD BLOOD GROUP
O	O	A, B
O	A	B, AB
O	B	A, AB
O	AB	AB
A	O	B
A	A	B, AB
B	O	A
B	B	A, AB
AB	O	O
AB	A	O
AB	B	O

*Impossible mother-child combinations are not included.

The application of these laws in forensic medicine is extremely simple. If a man is alleged to be the father of an illegitimate child, it is only necessary to test his blood, the blood of the child and the blood of the mother. If the mother is Group O, the alleged father Group O, and the child Group A and Group A antigen is not present in the blood of the alleged father or of the mother, it could not have come from the mother; it must have come from the real father of the child. Therefore, it may be concluded that the alleged father is not the natural father.

On the other hand, if the mother and the alleged father are Group A and the child is Group O, this does not prove that the alleged father is not the real father of the child, because persons of Group A sometimes produce children of Group O (Table 1). The O factor seems to act as a recessive in the presence of A or B. If these simple rules are kept in mind, little difficulty will be encountered in interpreting the results.

In performance of the tests it is naturally very important that the blood be correctly identified at the time it is taken. Sufficient blood may be taken by puncture of the finger or earlobe of the man and woman and put into physiologic saline solution. With very young children puncture of the great toe seems preferable.

The A and B antigens are not the only ones that may be applied to the investigation of paternity.

The inheritance of the M and N factors (Table 2), discovered in 1927, is equally well known.

The rules of inheritance are somewhat simpler because there is nothing corresponding to Type O — that is, either antigen M or antigen N, or both, is always present in the blood. The interpretation of the test is otherwise exactly the same.

The Rh factors, discovered in 1940, have been investigated sufficiently so that they are being used by some workers in cases of disputed parentage. Eight genes are thought to be involved in the inheritance of the Rh factors, and since the resulting combinations of these genes, 2 at a time, give a possible 36 genotypes, not all of which can be distinguished by the use of the serums at present available or even by the use of any serums that may eventually be available, it is not so easy to summarize the interpretation of tests for the Rh factors in cases of disputed parentage. Weiner's summary of the situation is as follows:

TABLE 2. *Exclusion of Paternity on the Basis of Characteristics M and N.*

CHILD CHARACTERISTIC	MOTHER CHARACTERISTIC	FATHER NOT POSSIBLE CHARACTERISTIC
M	M or MN	N
N	N or MN	M
MN	M	M
MN	N	N

> Factors Rh_O, rh′, rh″, hr′ and hr″ cannot appear in the blood of a child unless present in the blood of one or both parents.
>
> Parents of types Rh_1Rh_1 and rh′rh′ cannot have children of types rh, Rh_O, Rh_2 or rh″, and parents of types rh, Rh_O, Rh_2 and rh″ cannot have children of types Rh_1Rh_1 or rh′rh′. Or, more simply, hr′-negative parents cannot have rh′-negative children, and rh′-negative parents cannot have hr′-negative children.
>
> Parents of types Rh_2Rh_2 and rh″rh″ cannot have children of types rh, Rh_O, Rh_1 and rh′, and vice versa. Or, more simply, hr″-negative parents cannot have rh″-negative children, and rh″-negative parents cannot have hr″-negative children.

WILLIAM C. BOYD, M.D.
Professor of Immunochemistry, Boston University School of Medicine.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR SEPTEMBER, 1949

RÉSUMÉ

DISEASES	SEPTEMBER 1949	SEPTEMBER 1948	SEVEN-YEAR MEDIAN
Chancroid	2	2	1*
Chicken pox	85	135	114
Diphtheria	7	27	11
Dog bite	1009	980	924
Dysentery, bacillary	5	9	11
German measles	48	58	56
Gonorrhea	292	303	410
Granuloma inguinale	1	0	0*
Lymphogranuloma venereum	1	1	1*
Malaria	1	1	13
Measles	48	203	150
Meningitis, meningococcal	2	4	6
Meningitis, Pfeiffer-bacillus	0	2	1
Meningitis, pneumococcal	0	1	1
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	1	0
Meningitis, undetermined	2	6	4
Mumps	173	351	194
Poliomyelitis	608	55	121
Salmonellosis	7	2	20
Scarlet fever	56	105	190
Syphilis	155	141	352
Tuberculosis, pulmonary	196	200	205
Tuberculosis, other forms	8	14	15
Typhoid fever	0	1	2
Undulant fever	2	4	2
Whooping cough	463	268	520

*Five-year median.

COMMENT

Diseases above the seven-year median for September were dog bite and poliomyelitis.

Diseases below the seven-year median were chicken pox, German measles, measles, mumps, salmonellosis, scarlet fever and whooping cough.

Poliomyelitis continued at a high level, exceeding all records for September except 1916. If only paralytic cases were counted, however, the figures this year were far below 1916.

Although chicken pox was unusually prevalent during the first half of this year, it fell to the lowest level for this month since 1939.

Measles also ran unusually high during the early part of this year, but the number of cases fell to the lowest September since 1937.

Scarlet fever, for the past three months, has been at the lowest levels ever recorded.

GEOGRAPHIC DISTRIBUTION OF CERTAIN DISEASES

Actinomycosis was reported from: New Bedford, 1; total, 1.

Diphtheria was reported from: Boston, 1; Chelsea, 1; Foxboro, 1; Lenox, 1; Malden, 1; Rockport, 1; Somerville, 1; total, 7.

Dysentery, amebic, was reported from: North Andover, 1; total, 1.

Dysentery, bacillary, was reported from: Boston, 4; Brookline, 1; total, 5.

Encephalitis, infectious, was reported from: New Bedford, 1; Salisbury, 1; total, 2.

Lymphocytic choriomeningitis was reported from: Springfield, 1; total, 1.

Malaria was reported from: Medford, 1; total, 1.

Meningitis, meningococcal, was reported from: Brockton, 1; Malden, 1; total, 2.

Meningitis, undetermined, was reported from: Haverhill, 1; Worcester, 1; total, 2.

Poliomyelitis was reported from: Abington, 1; Adams, 1; Amesbury, 2; Amherst, 3; Arlington, 11; Ashby, 3; Ashland, 1; Attleboro, 4; Auburn, 1; Ayer, 1; Barnstable, 2; Bellingham, 1; Belmont, 1; Berlin, 1; Beverly, 8; Billerica, 2; Boston, 87, Braintree, 6; Brewster, 1; Brockton, 5; Brookline, 10; Burlington, 1; Cambridge, 5; Canton, 3; Carver, 1; Charlton, 2; Chelsea, 7; Chicopee, 1; Clinton, 1; Cohasset, 1; Concord, 4; Dalton, 1; Dedham, 4; Dennis, 1; E. Bridgewater, 3; Everett, 15; Fairhaven, 1; Fall River, 6; Falmouth, 6; Fitchburg, 6; Framingham, 3; Franklin, 1; Great Barrington, 1; Groveland, 1; Hampden, 1; Hanover, 2; Hardwick, 1; Hatfield, 1; Haverhill, 5; Hingham, 4;

Holbrook, 1; Holden, 3; Holyoke, 3; Hudson, 1; Ipswich, 2; Kingston, 1; Lancaster, 4; Lawrence, 2; Lee, 2; Lenox, 1; Leominster, 5; Lexington, 4; Longmeadow, 2; Lowell, 1; Ludlow, 1; Lynn, 24; Malden, 7; Manchester, 2; Mansfield, 6; Marblehead, 3; Marion, 2; Marlboro, 1; Marshfield, 1; Medford, 15; Melrose, 17; Mendon, 2; Methuen, 1; Middleboro, 1; Milford, 1; Millis, 1; Milton, 3; Montague, 1; Nahant, 1; Natick, 4; Needham, 3; New Bedford, 6; Newburyport, 3; Newton, 11; North Attleboro, 2; North Brookfield, 2; North Reading, 3; Northampton, 2; Norton, 2; Norwell, 2; Norwood, 4; Palmer, 3; Peabody, 3; Pembroke, 2; Pittsfield, 10; Plymouth, 3; Quincy, 19; Randolph, 4; Reading, 4; Revere, 5; Rochester, 1; Rockland, 4; Salem, 7; Savoy, 1; Scituate, 1; Sharon, 5; Shirley, 3; Shrewsbury, 1; Somerville, 9; South Hadley, 1; Southboro, 2; Spencer, 1; Springfield, 4; Stockbridge, 1; Stoughton, 2; Stow, 1; Swampscott, 2; Swansea, 1; Taunton, 2; Tewksbury, 1; Townsend, 1; Truro, 1; Wakefield, 5; Walpole, 1; Waltham, 13; Watertown, 5; Wellesley, 3; West Boylston, 1; West Springfield, 1; Westfield, 3; Westford, 2; Westminster, 4; Weston, 1; Westport, 3; Westwood, 1; Weymouth, 6; Winchendon, 2; Winchester, 4; Winthrop, 6; Woburn, 4; Worcester, 30; Wrentham, 1; total, 608.

Salmonellosis was reported from: Boston, 3; Lexington, 2; Lowell, 1; Marblehead, 1; total, 7.

Septic sore throat was reported from: Boston, 3; Westford, 1; Worcester, 1; total, 5.

Trichinosis was reported from: Boston, 2; Brockton, 1; Malden, 2; Plymouth, 1; Worcester, 3; total, 9.

Undulant fever was reported from: Great Barrington, 1; Holden, 1; total, 2.

MISCELLANY

AN APPEAL TO WHO

The editors of *Ärztliche Praxis*, a German weekly medical journal devoted to the interests of the general practitioner, have directed an open letter for help to Dr. Brock Chisholm, director general of the World Health Organization.

The appeal is based on the surplus of skilled physicians in the three western zones of Germany and their lack in many other parts of the world, and the desire that the World Health Organization may facilitate the emigration of these trained physicians into less favored areas.

CORRESPONDENCE

LAST REBUTTAL

To the Editor: Dr. Allan M. Butler's letter in the October 13 issue of the *Journal* hints that Dr. McManamy's aversion to "therapeutic" abortion, euthanasia and so forth is used as an "out" in avoiding difficult problems. It seems to me that euthanasia and "therapeutic" abortions are definite acts performed expressly to avoid difficult problems.

I suggest that Dr. Butler should find out what "good Catholicism" means before he uses the term.

Unlike many things, the Fifth Commandment has no exceptions.

FRANCIS D. MCCARTHY, M.D.

Melrose, Massachusetts

BOOK REVIEWS

A Treatise on Obstetric Labor. By Richard Torpin, M.D. With a chapter on erythroblastosis fetalis and the Rh factor, by Edith L. Potter, M.D., and Philip Levine, M.D. 8°, cloth, 590 pp., with 187 illustrations. Augusta, Georgia: Augusta Obstetric and Gynecologic Book Company, 1949. $7.00.

This treatise on obstetric labor is dedicated to the praiseworthy proposition that there are far too many operative deliveries, and that a much larger percentage of labor should be normal. This, the author believes, can be accomplished by a judicious use of fluids, dextrose, transfusions, oxygen, sedation and rest, and in thousands of cases he has found these measures "far more profitable in saving life and preventing disability of mother and fetus than surgical treatment immediately and ever so skilfully done."

In a series of 41 chapters and 73 selected illustrative case reports he undertakes to demonstrate this proposition. As a result of his experience, he has almost entirely eliminated from his practice bagging, extraction and version, though rather surprisingly he performs episiotomy in almost every case, including normal deliveries. This conservative attitude, which he attributes to his early training by Culbertson and Heaney at Rush Medical College, is at least a refreshing contrast to much modern radical surgical obstetric teaching.

There is an authoritative chapter on erythroblastosis fetalis and the Rh factor by Dr. Edith L. Potter and Dr. Philip Levine. The work is illustrated with 187 admirable figures. Twelve hundred references to the literature are distributed in appropriate bibliographic groups at the close of the chapters.

Gynecologic Diagnosis. By Robert Tauber, M.D. 8°, cloth, 275 pp., with 80 illustrations. New York: Thomas Nelson and Sons, 1949. $5.00.

This monograph is intended to teach students correct methods of gynecologic diagnosis. The author first discusses history taking and interpretation, the various technics of physical examination, the essential laboratory tests and the common diagnostic surgical procedures. He then presents what he terms a diagnostic clinic, a series of 33 cases in six groups, illustrating a number of frequent and a few rare pathologic conditions. At no time is the diagnosis stated, but the reader is supposed to make his own and then to refer to a list at the end of the book. There is an excellent final chapter on errors in diagnosis, and their avoidance. The work is admirably illustrated with eighty full-page figures by C. W. Brill, and has a brief bibliography of seventeen appropriate special references.

Die Kreuzschmerzen der Frau ihre Deutung und Behandlung. Gynäkologische Orthopädie. By Professor Dr. Heinrich Martius, director of the University Women's Clinic, Göttingen. Third edition. 8°, paper, 136 pp., with 64 illustrations by Käthe Droysen. Stuttgart: Georg Thieme, 1947. Imported by Grune and Stratton, Incorporated, New York. $2.75.

This third edition of a well known work, first published a decade ago, by the director of the Women's Clinic at Göttingen, presents an exhaustive survey of all the gynecologic conditions to which sacral pain in women is commonly attributed. Without denying the importance of these and of their appropriate treatment, the author believes that in all cases there is also an intrinsic postural element — that sacral, lumbosacral and sacroiliac pain in women is fundamentally an orthostatic symptom whose concurrent orthopedic treatment with a properly designed and adjusted girdle is essential, if satisfactory and total relief is to be obtained.

The book is well illustrated with 64 admirable black-and-white drawings by Käthe Droysen, and has an elaborate and valuable bibliography of 500 well selected references.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Surgery of the Eye. By Meyer Wiener, M.D., honorary consultant, ophthalmology, Bureau of Medicine and Surgery, United States Navy. Second edition. 8°, cloth, 426 pp., with 426 illustrations. New York: Grune and Stratton, 1949. $12.00.

In this second edition a special illustrated work on surgery of the eye, first published in 1939 and long out of print, has been revised and brought up to date. The new material includes the preparation of sutures preliminary to the incision for cataract, Otto Barkan's improved technic for congenital glaucoma, Burch's method of implantation in evisceration and Wiener's method of transplantation of the cornea by means of a mechanically obtained beveled edge. The text is not padded with redundant references to the literature. There is a good index. The work is intended to be a handy atlas of operating procedures for the ophthalmologist.

Critical Studies in Neurology. By F. M. R. Walshe, M.D., F.R.S., F.R.C.P., physician to University College Hospital, physician to the National Hospital for Nervous Diseases, Queen Square, and fellow of University College, London. 8°, cloth, 256 pp., with 16 illustrations. Baltimore: Williams and Wilkins Company, 1948. $4.50.

The author has brought together in this small volume six papers originally published in *Brain* during the period 1942 to 1947, to which is added a paper published in the *British Medical Journal* in 1945. The series is preceded by an essay entitled "The Function of Criticism in Medicine." The reprinted papers comprise the anatomy and physiology of cutaneous sensibility; the giant cells of Betz, the motor cortex and the pyramidal tract; the mode of representation of movements in the motor cortex with special reference to "convulsions beginning unilaterally" (Jackson); the notion of the "discrete movement" in willed motion; the role of the pyramidal system in willed movements; and the integration of medicine. The publishing is well done. It is a convenience to have the scattered papers of Dr. Walshe brought together in one volume. It should be in the neurologic sections of medical libraries and available to neurologists.

Diseases of the Fundus Oculi: With atlas. By Adalbert Fuchs, M.D., e.o. professor of ophthalmology of the University of Vienna. Translated by Erich Pressburger, M.D. Edited by Abraham Schlossman, M.D. First English edition. 4°, cloth, 381 pp., with 81 illustrations and 44 tables. Philadelphia: Blakiston Company, 1949. $30.00.

It is a pleasure to note that this classic treatise of Professor Fuchs has been translated into English. The original German edition appeared in 1943, and in this edition in English the author has added many pictures and much material that had not appeared before either in German or in English, making it practically a new work. There are eighty figures in the text and the appended atlas consists of forty-four plates in color printed from the original plates in Vienna, and imported for inclusion in this volume. The plates are typical of the finest German work. There is a good index, and the type and printing are excellent. Dr. Fuchs is well known for his *Atlas of Histopathology of the Eye*, published in two volumes in 1923 and 1927. The edition is limited to 995 numbered copies. The price is not excessive for this type of book. The atlas should be in all eye collections in medical libraries and likewise available to all ophthalmologists.

NOTICES

COMBINED MEETING OF NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE AND MASSACHUSETTS CHAPTER OF AMERICAN PHYSICAL THERAPY ASSOCIATION

A combined meeting of the New England Society of Physical Medicine and the Massachusetts Chapter of the American Physical Therapy Association will be held in the Bigelow Amphitheater of the Massachusetts General Hospital on Wednesday, November 16, at 8 p.m.

Dr. Eugene E. Record will speak on the subject "The Amputee and His Rehabilitation," with lantern slides, motion pictures and case presentations. Dr. Arthur L. Watkins will lead the discussion.

Physicians, physical therapists, occupational therapists and corrective therapists are cordially invited to attend.

94TH INFANTRY DIVISION LECTURES

The 94th (Bay State) Infantry Division is sponsoring a series of monthly lectures by prominent physicians in their respective specialties. The eighth lecture will be held in the auditorium of Boston University School of Medicine, 80 East Concord Street, Boston, on Thursday, November 17, at 8 p.m.

Dr. Elvin Semrad will speak on the subject "Common Pitfalls in Psychotherapy."

All interested physicians, whether reserve officers or not, are cordially invited to attend this carefully planned program. Reserve officers will be given one point credit if authorized by the instructor of their unit of assignment. Excellent films will also be shown during this period.

MASSACHUSETTS PUBLIC HEALTH ASSOCIATION

The annual fall meeting of the Massachusetts Public Health Association will be held at Simmons College, 300 Fenway, Boston, on Thursday, November 17. The section meetings, which begin at 4 p.m., will include sessions of the sections of health officers, laboratory, sanitation, maternal and child health and public-health nursing, health education and food and nutrition. The dinner session will be held at 6 p.m. The feature of the general session, beginning at 7 p.m., will be a panel discussion, led by Dr. John F. Conlin, on the subject "How John Q. Boston Was Persuaded To Be X-Rayed," which will emphasize the need of community participation in the attainment of public-health objectives.

NORFOLK DISTRICT MEDICAL SOCIETY

A meeting of the Norfolk District Medical Society will be held at the Boston Medical Library, 8 Fenway, Boston, on Tuesday, November 22, at 8 p.m. The following medical and surgical program by the Lahey Clinic, with Dr. Frank H. Lahey in charge, will be presented:

The Selection of Patients for Sympathectomy for Hypertension (Including Results after Operation). Dr. James A. Evans.
The Management of Ulcerative Colitis. Dr. Everett D. Kiefer.
Blood Diseases Related to the Spleen, and Indications for Splenectomy. Dr. John W. Norcross.
Recent Advances in the Management of Thyroid Diseases. Dr. Frank H. Lahey.

There will be a short business meeting.

Subsequent meetings will be held on Tuesday, January 24, Tuesday, February 28, Tuesday, March 28 and Wednesday, May 3 (annual dinner).

JOINT MEETING OF ALPHA OMEGA ALPHA AND BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

A lecture will be given under the joint sponsorship of the Harvard Chapter of Alpha Omega Alpha and the Boston City Hospital House Officers' Association in the auditorium of Building E, Harvard Medical School, on Tuesday, November 22, at 5 p.m.

The lecture will be on "Compound E in Arthritis" and will be delivered by Dr. Philip S. Hench, head of section in Division of Medicine, Mayo Clinic, and associate professor of medicine, The Mayo Foundation.

WORCESTER COUNTY CHAPTER, MASSACHUSETTS HEART ASSOCIATION

A panel discussion sponsored by the Worcester County Chapter of the Massachusetts Heart Association will be held at Dean Hall, Worcester, on Tuesday, November 22 at 8 p.m. The subject will be "The Problem of the Cardiac in Industry."

Howard B. Sprague, M.D., of Boston, president-elect of the American Heart Association, will be chairman of the panel. The panel speakers will include Eugene H. Giroux, chairman of the Massachusetts Industrial Accident Board, Karl Benedict, M.D., industrial physician, Norton Company, Worcester, who will speak on the subject "The Viewpoint of an Industrial Physician," and two members of the Worcester County Bar Association, who will present legal angles.

AMERICAN ACADEMY OF DERMATOLOGY AND SYPHILOLOGY

The eighth annual meeting of the American Academy of Dermatology and Syphilology will be held in Chicago from December 3 through December 8.

The principal sessions will be held at the Palmer House, with special courses in histopathology and mycology scheduled for Saturday and Sunday, December 3 and 4, at the medical schools of the University of Illinois and Northwestern University. Teaching clinics will be held at the University of Illinois College of Medicine in Chicago on the afternoons of December 5, 6 and 7.

(*Notices concluded on page xvii*)